Nephrol Dial Transplant (2014) 29: 2260–2268
doi: 10.1093/ndt/gfu234
Advance Access publication 30 June 2014

The urinary proteome as correlate and predictor of renal function in a population study

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ORIGINAL ARTICLE

ABSTRACT

Background. We investigate whether the urinary proteome refines the diagnosis of renal dysfunction, which affects over 10% of the adult population.

Methods. We measured serum creatinine, estimated glomerular filtration rate (eGFR) and 24-h albuminuria in 797 people randomly recruited from a population. We applied capillary electrophoresis coupled with mass spectrometry to measure multi-dimensional urinary proteomic classifiers developed for renal dysfunction (CKD273) or left ventricular dysfunction (HF1 and HF2). Renal function was followed up in 621 participants and the incidence of cardiovascular events in the whole study population.

Results. In multivariable-adjusted cross-sectional analyses, higher biomarker levels analysed separately or combined by principal component analysis into a single factor (SF), correlated ($P \leq 0.010$) with worse renal function. Over 4.8 years, higher HF1 and SF predicted ($P \leq 0.014$) lowering of eGFR; higher HF2 predicted ($P \leq 0.049$) increase in serum creatinine and decrease eGFR. HF1, HF2 and SF predicted progression from CKD Stages 2 or ≤2 to Stage ≥3, with risk estimates for a 1-SD increment in the urinary biomarkers ranging from 38 to 71% ($P \leq 0.039$). HF1, HF2 and SF yielded a net reclassification improvement of 31–51% ($P \leq 0.029$). Over 6.1 years, 47 cardiovascular events occurred. HF2 and SF, independent of baseline eGFR, 24-h albuminuria and other covariables were significant predictors of cardiovascular complications with risk estimates for 1-SD increases ranging from 32 to 41% ($P \leq 0.047$).

Conclusions. The urinary proteome refines the diagnosis of existing or progressing renal dysfunction and predicts cardiovascular complications.

Keywords: chronic kidney disease, eGFR, population science, renal function, urinary proteomics

INTRODUCTION

Chronic kidney disease (CKD) is becoming a major health problem affecting the quality of life of millions of people and draining health care resources. In the USA, CKD defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 increased from 10.0% in 1988–94 to 13.1% in 1999–2004 [1]. Furthermore, the Global Burden of Disease Study 2010 collaboration estimated that worldwide 0.403 million of nearly 50 million deaths occurring annually, were attributable to CKD in 1990 and 0.736 in 2010, representing an increase by 82.3% [2]. Across all ages, over the same time span, the years lived with CKD increased by 57.1% from 2.56 to 4.02 million [3], while the disability-adjusted life years, a metric that captures both premature mortality and the prevalence of ill-health increased by 51.7% from 13.9 to 21.2 million [4]. Diagnosis of CKD before eGFR starts declining and prediction of CKD is therefore of paramount importance in the prevention of

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irreversible renal dysfunction that often progresses to end-stage renal failure and causes cardiovascular complications and premature death [3, 4].

Recent publications proved the feasibility to develop multi-dimensional classifiers based on the urinary proteome that are associated with CKD [5, 6], and left ventricular dysfunction [7], but they were mainly derived in CKD patients matched with controls [8–10] or in patient cohorts with diabetes [5] or CKD [6]. In the current study, we investigated the performance of these biomarkers [5–7] in a general population. We assessed their association cross-sectionally and longitudinally in relation to renal function, and prospectively in relation to the incidence of cardiovascular complications.

MATERIALS AND MEHODS

Study population

The Ethics Committee of the University of Leuven approved the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO) [11, 12]. Recruitment started in 1985 and continued until 2004. The initial participation rate was 78.0%. The participants were repeatedly followed up [11, 12]. From May 2005 to May 2010, we mailed an invitation letter to 1208 former participants for a follow-up examination. However, 153 were unavailable, because they had died ($n = 26$), had been institutionalized or were too ill ($n = 27$), or because they had moved out of the area ($n = 100$). Of the remaining 1055 former participants, 828 renewed informed consent. The participation rate was therefore 78.5%. We excluded 31 participants from the cross-sectional analyses, because either no urine ($n = 22$) or no blood sample ($n = 9$) was available. Thus, the number of participants statistically analysed totalled 797, of whom 621 (77.9%) participated in the follow-up of renal function.

Assessment of renal function and biochemical variables

We measured the concentration of creatinine in serum, using Jaffe's method [13], with modifications described elsewhere [14, 15], on automated analysers in a single-certified laboratory. We assessed renal function from serum creatinine, eGFR computed by the Modification of Diet in Renal Disease (MDRD) [16] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [17] equations. CKD stages, defined according to the National Kidney Foundation KDOQI guideline, were eGFR ≥90, 60–89, 45–59, 30–44, 15–29 and <15 mL/min/1.73 m^2 for Stage 1, 2, 3A, 3B, 4 and 5, respectively (http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm).

At baseline, we also measured blood glucose, serum total and high-density (HDL) cholesterol, serum γ-glutamyltransferase as an index of alcohol intake, and micro-albumin in 24-h urine collections. Diabetes mellitus was a self-reported diagnosis, a fasting glucose level of at least 126 mg/dL, or use of antidiabetic agents [18]. Micro-albuminuria was a 24-h urinary excretion ranging from 30 to 300 mg and macro-albuminuria a 24-h excretion exceeding 300 mg.

Proteomic classifiers

The Supplementary data (pages 2–4) gives detailed information on the preparation and processing of urine samples. Peptide fragments identified in previous studies [7, 8] were combined into a single summary variable, using the support-vector machine-based MosaCluster software, version 1.6.5. In the present study, we used CKD273 as a multi-dimensional classifier based on 273 urinary peptide biomarkers that were significantly associated with CKD [8]. We also assessed two multi-dimensional classifiers associated with decreased left ventricular function and based on 85 (HF1) [7] and 671 (HF2) urinary peptide fragments. The peptide fragments included in CKD273 [8] have been published. The Supplementary data provide information on the peptide fragments making up HF1 (Supplementary data, Table S1) and HF2 (Supplementary data, Table S2), the peptides with known amino-acid sequence included in HF1 (Supplementary data, Table S3) and HF2 (Supplementary data, Table S4), and on the characteristics of 20 peptides shared by CKD273, HF1 and HF2 (Supplementary data, Table S5).

Other measurements

At the examination centre, nurses administered a questionnaire to collect detailed information on each participant's medical history, smoking and drinking habits and intake of medications. The conventional blood pressure was the average of five consecutive auscultatory readings obtained with the subject in the seated position. The mean arterial pressure was diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure. Hypertension was a blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic or use of antihypertensive drugs. The body mass index was weight in kilograms divided by the square of height in meters.

Ascertainment of events

Via the National Population Registry in Brussels, Belgium, we ascertained vital status of all of the participants until 31 December 2012. We obtained the International Classification of Disease codes for the immediate and underlying causes of death from the Flemish Registry of Death Certificates. We also collected information on the incidence of non-fatal events via follow-up visits with repeat administration of the same standardized questionnaire.

Fatal and non-fatal cardiac events included myocardial infarction, acute coronary syndrome, new-onset angina (stable or unstable), chronic ischaemic heart disease, coronary revascularization, heart failure, new-onset atrial fibrillation and life-threatening arrhythmias. Fatal and non-fatal cardiovascular events comprised cardiac endpoints, stroke, transient ischaemic attack, aortic aneurysm, pulmonary heart disease, arterial embolism, peripheral arterial disease and revascularization of peripheral arteries. All events were adjudicated against the medical records of general practitioners or hospitals.

Statistical analysis

For database management and statistical analysis, we used the SAS system, version 9.3 (SAS Institute, Inc., Cary, NC, USA). Means were compared using the large-sample z-test or

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ANOVA and proportions by Fisher's exact test. We computed single correlation coefficients to assess unadjusted associations between variables. We searched for covariables of the renal function indices using a stepwise regression procedure with the P-values for variables to enter and stay in the models set at 0.15. We combined the three urinary proteomic variables into a single factor (SF), using the PROC FACTOR procedure implemented in the SAS software package with the method set to *principal* and rotation to *varimax*. Renal function and changes in renal function were analyses as continuous or categorical variables, using multivariable-adjusted linear regression, logistic regression and Cox modelling, as appropriate. We used Cox proportional hazard regression to model the incidence of death and cardiovascular complications as function of the baseline values of the proteomic biomarkers, renal function and other covariables. Finally, we assessed the added capacity of the urinary proteomic biomarkers to predict worsening of renal function, using the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) [19, 20]. IDI is the difference between the discrimination slopes of basic models and basic models extended with the urinary biomarker of interest. The discrimination slope is the difference in predicted probabilities (%) between cases and controls. We calculated the continuous NRI as described by Pencina *et al.* [21]. First, we predicted in each subject the 5-year risk for a worsening in renal dysfunction from a Cox proportional hazards model with and without the biomarker included. NRI is then calculated as $2 \times [P(up|case) - P(up|noncase)]$. P(up|case) is the percentage of subjects with a worsening in renal dysfunction, whose predicted probability is increased by adding the biomarker to the model. Likewise, P(up|noncase) is the percentage of subjects without a worsening in renal function, whose predicted probability is increased by adding the biomarker.

RESULTS

Characteristics of participants

Age averaged 51.0 years (range 18–89 years) and the proportion of women was 50.7%. Of 797 participants, 338 (42.4%) had hypertension, of whom 207 (61.2%) were on antihypertensive drug treatment, and 9 (1.1%) had diabetes. Among 207 patients on treatment with antihypertensive drugs, 82 (39.6%) used diuretics, 168 (81.2%) used inhibitors of the renin system (β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and 40 (19.3%) were on treatment with vasodilators (calcium channel blockers or α-blockers). Among treated patients 78 (37.7%) were on combination therapy with >1 drug class.

Table 1 lists the characteristics of participants by quartiles of the distribution of CKD273. Age, body mass index, central obesity, systolic and mean arterial blood pressure, the prevalence of hypertension and total cholesterol increased ($P \leq 0.006$) with higher category of CKD273. Among all participants, 29 (3.6%) had micro-albuminuria and 3 (0.4%) had macro-albuminuria. Renal function as assessed by serum creatinine, eGFR or 24-h urinary albumin excretion decreased ($P < 0.0001$) with higher CKD273 category. The prevalence of micro-albuminuria increased across the quartiles of the CKD273 distribution ($P < 0.0001$) with frequencies of 0.5% ($n = 1$), 1.5% ($n = 3$), 3.0% ($n = 6$) and 9.6 ($n = 19$), respectively. Macro-albuminuria occurred only in the top CKD273 quartile. The proportion of women, smokers, consumers of alcohol, diabetic patients and average heart rate did not differ ($P \geq 0.20$) across CKD273 categories. Supplementary data, Figure S1 displays the distributions of the urinary proteomic markers. Figure 1 gives the distributions of the renal function indices at baseline and follow-up.

Combination of proteomic biomarkers into a SF

The correlations of CKD273 with HF1 and HF2 were 0.47 and 0.45 ($P < 0.0001$), while that between HF1 and HF2 was 0.76 ($P < 0.0001$). To avoid collinearity in models including more than one biomarker, we derived an SF (eigenvalue, 2.13) as a linear combination of CKD273, HF1 and HF2. SF had high loadings on CKD273 ($r = 0.73$), HF1 ($r = 0.90$) and HF2 ($r = 0.89$).

Cross-sectional association of renal function with urinary proteomic markers

Continuous measures of renal function. The covariables identified by stepwise regression analysis are given in Supplementary data, Table S6, page 5. With adjustments for these covariables applied (Table 2), serum creatinine increased with CKD273 and SF ($P \leq 0.010$), whereas eGFR decreased with all four proteomic biomarkers ($P \leq 0.010$). The 24-h urinary albumin excretion increased ($P \leq 0.006$) with all urinary proteomic biomarkers. The effect sizes for 1-SD increment were 8.9% [95% confidence interval (CI): 6.5, 11.3] for CKD273, 3.4% (95% CI: 0.97, 5.8) for HF1, 5.9% (95% CI: 3.4, 8.6) for HF2 and 7.7% (95% CI: 5.1, 10.4) for SF.

Categorical measures of renal function. Categories according to eGFR derived from the MDRD formula [16], included 22.1% ($n = 176$) of participants for Stage 1, 70.0% for Stage 2 ($n = 558$), 6.9% for Stage 3A ($n = 55$), 0.9% for Stage 3B ($n = 7$) and 0.1% ($n = 1$) for Stage 4. Categories according to eGFR derived from the CKD-EPI formula [17], included 32.1% ($n = 256$) of participants for Stage 1, 59.5% ($n = 474$) for Stage 2, 6.8% ($n = 54$) for Stage 3A, 1.4% ($n = 11$) for Stage 3B and 0.2% ($n = 2$) for Stage 4.

Table 3 shows that irrespective of the eGFR formula applied, all odds ratios reached significance ($P \leq 0.05$) for all four urinary biomarkers for the risk of having a worse renal function, comparing Stages 2, ≥2, or ≥3 with Stage 1 or comparing Stage ≥3 with Stage 2. Furthermore, the risk of having a 24-h albuminuria of 30 mg or more increased ($P \leq 0.019$) with higher scores of the four biomarkers. The odds ratios associated with a 1–SD increment of the biomarker were 3.63 (95% CI: 2.31, 5.72) for CKD273, 1.63 (95% CI: 1.08, 2.46) for HF1, 2.20 (95% CI: 1.44, 3.36) for HF2 and 2.83 (95% CI: 1.81, 4.42) for SF.

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Table 1. Baseline characteristics of 797 participants by fourths of the CKD273 distribution

Characteristic	<−0.82	−0.82 to −0.61	−0.61 to −0.35	≥−0.35	P-value
Number of subjects (%)					
Women	100 (50.0)	99 (49.5)	103 (52.0)	102 (51.3)	0.96
Smokers	38 (19.0)	39 (19.5)	45 (22.7)	39 (19.6)	0.78
Drinking alcohol	140 (70.0)	138 (69.0)	140 (70.7)	135 (67.8)	0.93
Hypertension	57 (28.5)	90 (45.0)‡	82 (41.4)	109 (54.8)†	<0.0001
Antihypertensive treatment	35 (17.5)	46 (23.0)	46 (23.2)	80 (40.2)‡	<0.0001
Diabetes mellitus	1 (0.5)	3 (1.5)	2 (1.0)	3 (1.5)	0.80
Mean (SD) of characteristic					
Age (years)	45.2 (14.8)	48.6 (15.7)*	51.0 (14.6)	59.4 (14.2)§	<0.0001
Body mass index (kg/m^2)	26.3 (4.4)	25.7 (4.1)	26.4 (4.1)	27.5 (4.6)*	0.002
Waist-to-hip ratio	0.86 (0.09)	0.86 (0.08)	0.88 (0.08)†	0.89 (0.08)	<0.0001
Office blood pressure (mmHg)					
Systolic pressure	125.3 (15.1)	128.8 (17.3)*	129.7 (18.8)	133.8 (18.3)*	<0.0001
Diastolic pressure	78.5 (10.3)	80.5 (10.4)	79.6 (8.5)	80.0 (9.0)	0.22
Mean arterial pressure	94.1 (11.1)	96.6 (11.1)*	96.3 (10.2)	97.9 (10.2)	0.0009
Heart rate (b.p.m.)	64.2 (9.4)	63.4 (9.5)	63.4 (9.8)	62.9 (10.5)	0.20
Biochemical data					
Serum creatinine (μmol/L)	80.5 (13.9)	83.6 (14.4)*	83.8 (12.9)	88.1 (20.6)*	<0.0001
eGFR (MDRD, mL/min/1.73 m^2)	86.8 (19.0)	81.4 (14.7)†	79.5 (15.5)	73.5 (14.1)§	<0.0001
eGFR (CKD-EPI, mL/min/1.73 m^2)	89.9 (17.9)	84.6 (15.9)†	82.2 (16.4)	74.6 (15.9)§	<0.0001
24-h albuminuria (mg)	5.0 (3.7, 6.5)	5.2 (3.7, 6.7)	6.1 (4.5, 7.5)†	8.2 (5.1, 8.8)‡	<0.0001
Total cholesterol (mmol/L)	5.12 (1.01)	5.19 (1.00)	5.37 (0.99)	5.34 (0.88)	0.006
HDL cholesterol (mmol/L)	1.41 (0.34)	1.44 (0.36)	1.43 (0.36)	1.41 (0.34)	0.008
Total-to-HDL cholesterol ratio	3.80 (1.05)	3.77 (1.02)	3.93 (1.07)	3.97 (0.99)	0.046
Blood glucose (mmol/L)	4.90 (0.73)	4.89 (0.50)	4.92 (0.90)	5.04 (0.93)	0.073
γ-Glutamyltransferase (units/L)	22 (15, 30)	21 (14, 32)	23 (16, 31)	26 (16, 37)*	0.019

eGFR, estimated glomerular filtration rate calculated according to the MDRD or CKD-EPI formulas, as described in references [16] and [17], respectively. Office blood pressure was the average of five consecutive readings. Hypertension was an office blood pressure of ≥140 mmHg systolic, or ≥90 mmHg diastolic, or use of antihypertensive drugs. For 24-h albuminuria and γ-glutamyltransferase, values are the geometric mean (inter-quartile range). Conversion factors: creatinine from μmol/L to mg/dL, multiply by 0.0113; cholesterol from mg/dL to mmol/L, multiply by 0.0259.

P-values denote the significance of the differences in prevalence rates or means across quartiles of the CKD273 distribution. Significance of the difference with the adjacent lower fourth.

*$P \leq 0.05$.

†$P \leq 0.01$.

‡$P \leq 0.001$.

§$P \leq 0.0001$.

Longitudinal association of renal function with urinary proteomic predictors

Of 797 participants, 621 (77.9%) had their renal function indices reassessed after a median interval of 4.8 years (5–95th percentile interval: 3.7, 5.4).

Continuous measures of renal function. Over follow-up, serum creatinine increased by 5.74 μmol/L (95% CI: 4.59, 6.88; $P < 0.0001$), whereas eGFR according to the MDRD and CKD-EPI formulae decreased by 6.89 mL/min/1.73 m^2 (95% CI: 6.05, 7.74; $P < 0.0001$) and 7.68 mL/min/1.73 m^2 (95% CI: 6.89, 8.47; $P < 0.0001$), respectively (Figure 1).

In multivariable-adjusted analyses of the changes in renal function, we accounted for baseline renal function, follow-up duration and other covariables (Table 4). In general, higher scores of the urinary proteomic biomarkers with the exception of CKD273, predicted worsening of renal function. HF1 and SF predicted ($P \leq 0.014$) lowering of eGFR (MDRD and CKD-EPI). Higher HF2 predicted ($P \leq 0.049$) an increase in serum creatinine and a decrease eGFR (MDRD and CKD-EPI).

Categorical measures of renal function. Over follow-up (Supplementary data, Table S7), eGFR according to the MDRD formula remained at the same Stage in 458 (73.8%) participants, moved up in 139 (22.4%) and moved down in 24 (3.9%). According to the CKD-EPI formula, these numbers were 431 (69.4%), 167 (26.9%) and 23 (3.7%), respectively. No participant proceeded to CKD Stage 5 or renal replacement therapy.

In multivariable-adjusted Cox regression (Table 5), HF1, HF2 and SF, but not CKD273 ($P \geq 0.11$) predicted progression from CKD Stages 2 or ≤2 to Stage ≥3, irrespective of the formula used to estimate eGFR, with risk estimates for a 1–SD increment in the urinary biomarkers ranging from 38 to 71% ($P \leq 0.039$). Figure 2 provides the multivariable-adjusted risk functions for the progression of CKD from Stage ≤2 to ≥3.

Improvement of prognostic accuracy

For a decline in eGFR from Stage ≤ 2 to ≥ 3 based on the MDRD formula, IDI reached significance ($P \leq 0.032$) for HF2 and SF (Table 6). By applying the CKD-EPI formula, IDI was significant ($P \leq 0.043$) for HF1, HF2 and SF. Irrespective of the formula applied, the NRI was significant ($P \leq 0.029$) for HF1, HF2 and SF (Table 6).

Incidence of events

Among 797 participants who had their urinary proteome measured at baseline, the median follow-up was 6.11 years (5–95th percentile interval: 3.68, 7.36). Mortality included 8 cardiovascular and 13 non-cardiovascular deaths, and 6 deaths from

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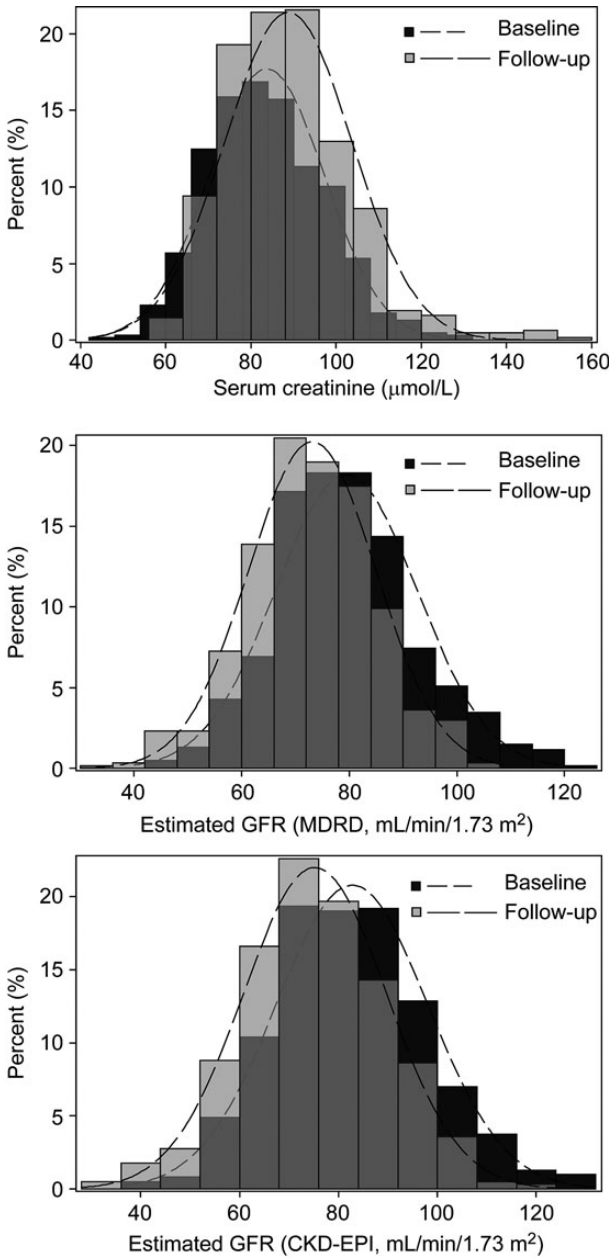

FIGURE 1: Distributions of the renal function indices at baseline and follow-up in 621 participants examined at baseline and follow-up.

undocumented causes. None of the biomarkers predicted total mortality ($P \geq 0.65$).

During the follow-up, 47 cardiovascular events occurred including 29 cardiac events (6 cases of heart failure). As shown in Supplementary data, Table S8, CKD273 did not predict these outcomes with hazard ratios for a 1–SD increase ranging from 1.14 to 1.23 ($P \geq 0.26$). Of the three other urinary proteomic biomarkers, HF1 was a weak predictor of all cardiovascular and cardiac events with hazard ratios for a 1–SD increase ranging from 1.28 to 1.41 ($0.049 \leq P \leq 0.074$). HF2 and SF significantly ($P \leq 0.047$) predicted the composite cardiovascular endpoint, irrespective of whether the model included baseline eGFR or 24-h albuminuria, or both. In fully adjusted models, including all covariables and both eGFR and 24-h albuminuria, the hazard ratios associated with a 1–SD increase were 1.40 (95% CI: 1.06, 1.89; $P = 0.018$) for HF2 and 1.32 (95% CI: 1.00, 1.74; $P = 0.047$) for SF.

DISCUSSION

To our knowledge, our current study is the first to assess the association of CKD with urinary proteomic biomarkers in a general population. The key findings can be summarized as follows: (i) in cross-sectional analyses, continuous measures of renal function and CKD stages correlated with CKD273, HF1, HF2 and SF; (ii) HF2 and SF predicted the incidence of cardiovascular complications; (iii) HF1, HF2 and SF predicted the changes of the renal function indices over time and progression of the CKD stage; (iv) optimized discrimination limits improved IDI and NRI for predicting the progression of renal dysfunction from the urinary proteomic biomarkers. NRI and IDI provide complimentary information. Indeed, adding a biomarker to a model might increase the predicted probability in cases, which means an increase in NRI, but perhaps only to a limited extend, as reflected by IDI.

Our current study moves beyond the available literature data, which were obtained in CKD patients matched with controls [8–10] or in patient cohorts with diabetes [5] or CKD ([6]). Good *et al.* derived CKD273 in a training database consisting of 609 patients with biopsy-proven CKD and 379 healthy controls [8]. Analysis of the urinary proteome yielded 634 peptides with significantly different signal between cases and controls. This set was subsequently reduced to 273 peptides with known sequence frequency. Good *et al.* reproduced in a blinded manner this biomarker pattern in an independent test database including 110 CKD patients and 34 controls. Upon unblinding, all controls and 94 patients with CKD were correctly classified, resulting in a sensitivity of 85.5% (95% CI: 77.5, 91.4) and a specificity of 100% (95% CI: 89.6, 100.0) [8].

The CKD273 proteomic marker was further studied in three prospective studies [5, 6, 9]. In a study of 44 patients with type 2 diabetes progressing to micro- or macro-albuminuria and 44 matched controls, the multivariable-adjusted odds ratio associated with CKD273 was 1.35 (95% CI: 1.02, 1.79) [9]. CKD273 significantly ($P = 0.002$) improved IDI over and beyond baseline urinary albumin excretion and eGFR [9]. In a study of 53 CKD patients, CKD273 increased with worse CKD stage and was linearly correlated with eGFR ($r = -0.64$; $P < 0.001$). Over 3.6 years of follow-up, four patients were lost to follow-up. The CKD273 score was >0.55 in all 15 patients who reached an endpoint, either dialysis ($n = 9$) or died ($n = 6$) [6]. None of the patients with a baseline CKD273 score <0.55 experienced an endpoint [6].

Several issues should be highlighted when comparing our current results with the published literature on CKD273 [5, 6, 8, 9]. First, findings in patients with advanced CKD or diabetes cannot be readily generalized to unselected people as enrolled in our population study. This might explain why in our present study the renal function indices were correlated with CKD273 in cross-sectional analyses, whereas in longitudinal analyses

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Table 2. Multivariable-adjusted associations of renal function with urinary proteomic biomarkers

Explanatory variables (SD)	Serum creatinine	eGFR (MDRD)	eGFR (CKD-EPI)
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
CKD273 (0.39)	1.57 (0.57, 2.58)†	−3.83 (−4.96, −2.69)§	−4.17 (−5.30, −3.04)§
HF1 (0.92)	0.86 (−0.16, 1.88)	−1.56 (−2.75, −0.38)†	−2.09 (−3.27, −0.90)‡
HF2 (0.62)	0.90 (−0.18, 1.99)	−2.47 (−3.70, −1.24)§	−3.24 (−4.46, −2.02)§
SF (1.0)	1.43 (0.34, 2.52)*	−3.26 (−4.49, −2.03)§	−3.96 (−5.18, −2.74)§

eGFR, estimated glomerular filtration rate calculated according to the MDRD or CKD-EPI formulae, as described in references [16] and [17], respectively. Estimates given with 95% CI, express the difference in renal function associated with a 1–SD increase in the proteomic biomarkers. All associations were adjusted for mean arterial pressure, waist-to-hip ratio, smoking, log γ-glutamyltransferase (index of alcohol intake), total-to-HDL cholesterol ratio, blood glucose, log 24-h albuminuria, and use of diuretics, vasodilators (calcium channel blockers and α-blockers) and inhibitors of the renin–angiotensin system (β-blockers, angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers). The association with serum creatinine was additionally adjusted for sex, age and body mass index. Significance of the associations.

$^{*}P \leq 0.05$.

$^{\dagger}P \leq 0.01$.

$^{\ddagger}P \leq 0.001$.

$^{\S}P \leq 0.0001$.

Table 3. Multivariable-adjusted associations of eGFR with urinary proteomic biomarkers

Biomarkers	Stage 2 versus Stage 1	Stage ≥3 versus Stage 1	Stage ≥2 versus Stage 1	Stage ≥3 versus Stage 2
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
MDRD				
CKD273	1.70 (1.37, 2.11)§	2.98 (1.80, 4.94)§	1.76 (1.42, 2.18)§	1.46 (1.09, 1.95)*
HF1	1.23 (1.00, 1.53)*	1.80 (1.18, 2.75)†	1.26 (1.02, 1.56)*	1.34 (1.01, 1.79)*
HF2	1.38 (1.09, 1.73)†	2.26 (1.43, 3.59)‡	1.42 (1.13, 1.79)†	1.36 (1.02, 1.80)*
SF	1.64 (1.28, 2.09)§	2.88 (1.70, 4.87)§	1.70 (1.33, 2.17)§	1.46 (1.10, 1.93)†
CKD-EPI				
CKD273	1.73 (1.41, 2.12)§	4.07 (2.42, 6.82)§	1.82 (1.49, 2.22)§	1.54 (1.16, 2.05)†
HF1	1.28 (1.06, 1.56)*	2.29 (1.47, 3.54)‡	1.32 (1.09, 1.60)†	1.35 (1.02, 1.77)*
HF2	1.50 (1.20, 1.86)‡	2.91 (1.86, 4.55)§	1.56 (1.26, 1.93)§	1.49 (1.13, 1.96)†
SF	1.74 (1.38, 2.19)§	3.97 (2.32, 6.78)§	1.83 (1.46, 2.29)§	1.53 (1.17, 2.01)†

eGFR, estimated glomerular filtration rate calculated according to the MDRD or CKD-EPI formulas, as described in references [16] and [17], respectively. Frequencies of the eGFR stages according to the MDRD and CKD-EPI are given in the Results section. Odds ratios, given with 95% CI, express the risk associated with a 1–SD increase in the proteomic biomarkers. All associations were adjusted for mean arterial pressure, waist-to-hip ratio, smoking, log γ-glutamyltransferase (index of alcohol intake), total-to-HDL cholesterol ratio, blood glucose, log 24-h albuminuria, and use of diuretics, vasodilators (calcium channel blockers and α-blockers) and inhibitors of the renin–angiotensin system (β-blockers, angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers). Significance of odds ratios.

$^{*}P \leq 0.05$.

$^{\dagger}P \leq 0.01$.

$^{\ddagger}P \leq 0.001$.

$^{\S}P \leq 0.0001$.

Table 4. Multivariable-adjusted association of renal function changes with baseline urinary proteomic biomarkers

Biomarker measured at baseline	Serum Creatinine	eGFR (MDRD)	eGFR (CKD-EPI)
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
CKD273	0.07 (−1.14, 1.27)	−0.34 (−1.09, 0.41)	−0.27 (−1.05, 0.50)
HF1	0.96 (−0.23, 2.15)	−1.02 (−1.75, −0.29)†	−0.95 (−1.71, −0.20)*
HF2	1.25 (0.01, 2.49)*	−1.34 (−2.09, −0.60)‡	−1.27 (−2.05, −0.50)†
SF	1.03 (−0.23, 2.29)	−1.18 (−1.94, −0.43)†	−1.11 (−1.90, −0.32)†

eGFR, estimated glomerular filtration rate calculated according to the MDRD or CKD-EPI formulas, as described in reference [16] and [17], respectively. Change in renal function was computed as follow-up minus baseline value. Estimates given with 95% CI, express the change in renal function associated with a 1–SD increase in the explanatory variables derived from the urinary proteome. SDs were 0.38 for CKD273; 0.91 for HF1; 0.59 for HF2; and 0.96 for SF. All associations were adjusted for baseline renal function and log urinary albumin, log-transformed follow-up time, mean arterial pressure, waist-to-hip ratio, smoking, blood glucose, log γ-glutamyltransferase, and total-to-HDL cholesterol ratio. Associations with changes in serum creatinine and creatinine clearance were additionally adjusted for sex, age and body mass index. Significance of the associations.

$^{*}P \leq 0.05$.

$^{\dagger}P \leq 0.01$.

$^{\ddagger}P \leq 0.001$.

$^{\S}P \leq 0.0001$.

CKD273 did not predict change in renal function or progression across stages of eGFR. Second, the published literature focused on CKD273 [5, 6, 8, 9]. However, CKD is a forerunner of heart failure and decline of left ventricular performance leads to renal dysfunction [22, 23]. We therefore assessed two multi-dimensional classifiers associated with left ventricular dysfunction. Third, we combined CKD273, HF1 and HF2 into SF. However, in longitudinal analyses, the biomarker combining

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Table 5. Multivariable-adjusted hazard ratios predicting changes in CKD stages in relation to the baseline urinary proteome

Endpoint	Rate (%)	Hazard ratios (95% CI)			
		CKD273	HF1	HF2	SF
MDRD					
Stage 2 → ≥3	49/456 (10.7)	1.29 (0.94, 1.77)	1.39 (1.02, 1.89)*	1.57 (1.17, 2.11)†	1.52 (1.13, 2.05)†
Stage ≤2 → ≥3	50/579 (8.64)	1.30 (0.94, 1.78)	1.45 (1.06, 1.98)*	1.71 (1.29, 2.26)‡	1.62 (1.21, 2.17)†
CKD-EPI					
Stage 2 → ≥3	54/388 (13.9)	1.18 (0.87, 1.59)	1.38 (1.03, 1.84)*	1.41 (1.06, 1.88)*	1.41 (1.06, 1.88)*
Stage ≤2 → ≥3	54/580 (9.31)	1.33 (0.98, 1.81)	1.53 (1.13, 2.05)†	1.58 (1.20, 2.08)†	1.61 (1.22, 2.13)‡

eGFR, estimated glomerular filtration rate calculated according to the MDRD or CKD-EPI formulas, as described in reference [16] and [17], respectively. Frequencies of the eGFR stages according to the MDRD and CKD-EPI are given in the Results section. Rate is the number of endpoints divided by number of participants at risk (%). Hazard ratios, given with 95% CI, express the increase in risk associated with a 1–SD increase in the explanatory variables derived from the urinary proteome. SDs were 0.38 for CKD273; 0.91 for HF1; 0.59 for HF2; and 0.96 for SF. All hazard ratios were adjusted for baseline values of mean arterial pressure, waist-to-hip ratio, smoking, blood glucose, log γ-glutamyltransferase, total-to-HDL cholesterol ratio and log 24-h albuminuria. Significance of the hazard ratios.

*$P \leq 0.05$.

†$P \leq 0.01$.

‡$P \leq 0.001$.

§$P \leq 0.0001$.

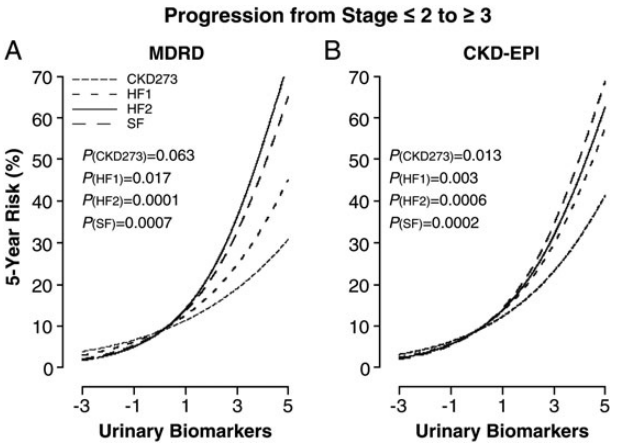

FIGURE 2: Five-year risk of progressing from CKD Stage ≤2 to stage ≥3 in 621 participants. CKD stages were based on the MDRD (A) or CKD-EPI (B) formula, as described in references [16] and [17]. To plot risk functions simultaneously for four biomarkers, we expressed the scores in units of standard deviation of the respective distributions. The risks were adjusted for baseline values of mean arterial pressure, waist-to-hip ratio, smoking, log γ-glutamyltransferase (index of alcohol intake), total-to-HDL cholesterol ratio, blood glucose and log 24-h albuminuria. P-values indicate the significance of the 5-year risks associated with the urinary biomarkers.

information from the three classifiers did not perform better than HF1 and HF2. Fourth, we assessed the incidence of cardiovascular and cardiac events in relation to the urinary proteomic biomarkers and noticed that HF2 and SF were significant predictors of such events, over and beyond covariables including baseline eGFR and 24-h urinary albuminuria.

Our current results reinforce the concept that dysfunction of the kidney and the left ventricle often co-exist [22–24]. Haemodynamic and non-haemodynamic mechanisms underpin the two-way interaction between the kidney and the heart [22, 23]. A decline in left ventricular systolic function and cardiac output activates the sympathetic nervous system and the renin–angiotensin system. The ensuing sodium and water retention and expansion of the circulating volume, although maintaining renal perfusion, increase afterload and can aggravate left ventricular dysfunction [22–24]. Left ventricular diastolic dysfunction with preserved ejection fraction may be accompanied with higher pressure in the central venous system [25], which in turn may increase renal intratubular pressure and reduce ultrafiltation pressure, thereby reducing glomerular filtration [26]. The drivers of the non-haemodynamic cardiorenal connection are the renin–angiotensin system, sympathetic nervous tone, inflammation and the balance between nitric oxide and reactive oxygen species [22]. Our study did not directly address the interaction between renal and left ventricular function, but might point to an avenue worthy of further research in predominantly asymptomatic people.

The present study must be interpreted within the context of some potential limitations. First, we determined proteinuria only at baseline and not at follow-up. However, in our view, 24-h albuminuria reflects microcirculatory organ damage rather than renal function. At baseline, this measure of target organ damage increased with all urinary proteomic biomarkers. In the Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes trial, micro-albuminuria developed in 8.2% of the patients in the olmesartan group and in 9.8% in the placebo group [27]. The incidence of microalbuminuria in our population study was presumably only a minor fraction of that observed in the high-risk ROADMAP patients, so that it is unlikely that we missed important information. Second, we lost 176 participants (22.1%) in the follow-up study of renal function. However, at baseline participants followed up and those not reassessed had similar distributions of female sex (49.9 versus 53.4%; P = 0.41), age (50.8 versus 51.8 years; P = 0.52) and previous cardiovascular disease (4.8 versus 6.3%; P = 0.45). Third, the renal function indices were only measured twice. However, Figure 1 shows the expected age-related shift, which excludes confounding by regression-to-the mean. Finally, CKD273 and HF1 shared 24 common peptide fragments, CKD273 and HF2 135 and HF1 and HF2 47. However, only 20 peptides were common to

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Table 6. NRI and IDI by adding the baseline urinary proteomic biomarkers to a model including covariables

	IDI			NRI		
	IDI (%)	CI (%)	P-value	NRI (%)	CI (%)	P-value
MDRD						
CKD273	0.82	0.00, 1.63	0.051	17.6	−11.4, 46.5	0.23
HF1	0.95	−0.36, 2.26	0.15	33.8	5.36, 62.2	0.020
HF2	2.54	0.65, 4.44	0.009	50.7	22.5, 78.8	0.0004
SF	2.00	0.17, 3.83	0.032	48.4	20.2, 76.5	0.0008
CKD-EPI						
CKD273	0.65	−0.15, 1.45	0.11	17.5	−10.5, 45.5	0.22
HF1	1.35	0.04, 2.65	0.043	30.8	3.09, 58.5	0.029
HF2	1.82	0.34, 3.30	0.016	46.6	19.3, 73.9	0.0008
SF	2.00	0.17, 3.83	0.032	48.4	20.2, 76.5	0.0008

Controls are participants not progressing from baseline to follow-up beyond CKD Stage 2. Cases are participants progressing from CKD ≤2 to ≥3. Models with and without biomarkers are compared. The reference models include as covariables baseline values of mean arterial pressure, waist-to-hip ratio, smoking, blood glucose, log γ-glutamyltransferase, total-to-HDL cholesterol ratio and log 24-h albuminuria (see Table 5). The IDI is the difference between the discrimination slopes of basic models and basic models extended with a predictor variable. The discrimination slope is the difference in predicted probabilities (%) between cases and controls. The NRI is the sum of the percentages of subjects reclassified correctly as cases and controls.

CKD273, HF1 and HF2. Moreover, the signal strength of shared polypeptides differed between classifiers, suggesting that the classifiers provided complimentary rather than duplicate diagnostic information. Supplementary data, Table S5 illustrates the differences in signal intensity for 20 polypeptides common to CKD273, HF1 and HF2.

CONCLUSION

The urinary proteome refines the diagnosis of already existing or progressing renal dysfunction. Our current findings extend previous reports including patients with CKD or diabetes mellitus [5, 6, 8, 9] to the general population, thereby providing a proof of concept in people at low risk. However, further studies are required to port our observation to clinical practice. Prospective studies in other populations should confirm our current findings and randomized clinical trials should demonstrate that the urinary proteome changes in parallel with the response to treatment. Having these research goals materialized would be a major step forward in view of the high prevalence of CKD, which in several countries currently affects over 10% of the adult population [28, 29].

SUPPLEMENTARY MATERIAL

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contribution of the nurses working at the examination centre (Linda Custers, Marie-Jeanne Jehoul, Daisy Thijs and Hanne Truyens) and the clerical staff at the Studies Coordinating Centre (Sandra Covens and Annick De Soete).

FUNDING

The European Union (HEALTH-2011.2.4.2–2-EU-MASCARA, HEALTH-F7-305507 HOMAGE and the European Research Council Advanced Researcher Grant-2011-294713-EPLORE) and the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (G.0881.13 and G.088013) currently support the Studies Coordinating Centre in Leuven.

CONFLICT OF INTEREST STATEMENT

T.K., P.Z. and H.M. are employees of Mosaiques-Diagnostics GmbH. None of the other authors declares a conflict of interest.

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Received for publication: 6.5.2014; Accepted in revised form: 3.6.2014

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ORIGINAL ARTICLE

Nephrol Dial Transplant (2014) 29: 2268–2277
doi: 10.1093/ndt/gfu249
Advance Access publication 21 July 2014

Adiponectin receptor and adiponectin signaling in human tissue among patients with end-stage renal disease

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ABSTRACT

Background. Adiponectin plasma levels in chronic kidney disease (CKD) are two to three times higher than in individuals with normal kidney function. Despite adiponectin's anti-diabetic, anti-inflammatory and anti-atherogenic properties, patients with CKD have insulin resistance, systemic inflammation and accelerated atherogenesis. Hence, although adiponectin production is increased by adipose tissue in end-stage renal disease (ESRD), it is unclear if its effects on metabolism remain intact.

Methods. To determine if there is adiponectin resistance in ESRD, we measured tissue levels of adiponectin receptor-1 (AdipoR1) and adiponectin downstream effectors in ESRD patients compared with normal kidney function controls. Blood and tissue samples were obtained from participants at the time of kidney transplantation or kidney donation. A follow-up blood sample was obtained 3–6 months after transplantation.

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Nephrology, Dialysis and Transplantation

Supplementary data

This appendix formed part of the original submission and has been peer reviewed.
Supplement to: The urinary proteome as correlate and predictor of renal function in a population study.
Nephrology, Dialysis and Transplantation 2014; published online *date*
http:/dx.doi.org/number.

Urinary proteomics

Preparation and processing of the urine samples

Participants collected 24–h urine samples within one week of the examinations. Using 24–h urine samples rather than spot urine samples minimizes the small influence of food intake during the day on the urinary proteome [3]. Aliquots were stored at –80 °C. Urine (0.7 mL) was thawed immediately before analysis and diluted with 0.7 mL of 2 M urea, 10 mM NH4OH containing 0.02% SDS [4]. To remove higher molecular mass proteins, such as albumin and immunoglobulin G, the sample was ultra-filtered using Centrisart ultracentrifugation devices (20 kDa MWCO; Sartorius, Göttingen, Germany) at 3,000 g relative centrifugal force until 1.1 mL of filtrate was obtained. This filtrate was then applied onto a PD-10 desalting column (GE Healthcare, Uppsala, Sweden) equilibrated in 0.01% NH4OH in HPLC-grade H2O (Roth, Germany) to decrease matrix effects by removing urea, electrolytes, and salts, and to enrich polypeptides. Finally, all samples were lyophilized, stored at 4 ºC, and suspended in HPLC-grade H2O shortly before CE-MS analyses [5].

CE-MS analyses were performed using a P/ACE MDQ capillary electrophoresis system (Beckman Coulter, Fullerton, USA) on-line coupled to a micrOTOF MS (Bruker Daltonic, Bremen, Germany) [5]. The ESI sprayer (Agilent Technologies, Palo Alto, CA, USA) was grounded, and the ion spray interface potential was set between -4 and -4.5 kV. Data acquisition and mass spectrometry acquisition methods were automatically controlled by the capillary electrophoresis via contact-close-relays. Spectra were accumulated every 3 s, over a range of charge states (m/z) 350 to 3000. Previous publications described the accuracy, precision, selectivity, sensitivity, reproducibility, and stability of the CE-MS measurements in detail [6].

Mass spectra were processed using MosaiquesVisu software, including peak picking, deconvolution and deisotoping [7]. Migration time and peak intensity were normalized using

internal polypeptide standards [8]. These fragments result from normal biological processes and appear to be unaffected by any disease state studied to date based on over 20000 samples in the Mosaiques database [9]. The resulting peak list characterizes each polypeptide by its molecular mass, normalized capillary electrophoresis migration time, and normalized signal intensity. All detected polypeptides were deposited, matched, and annotated in a Microsoft SQL database, allowing further analysis and comparison of multiple patient groups.

Proteomic classifiers

Peptide fragments identified in previous studies were combined into a single summary variable, using the support-vector machine based MosaCluster software, version 1.6.5. In the present study, we used CKD273 as a multidimensional classifier based on 273 urinary peptide biomarkers that were significantly associated with CKD [10]. Application of the CKD273 classifier results in a classification score, reflecting the similarity to the CKD-specific pattern. In selected small cohorts, CKD273 enabled prognosis of diabetic nephropathy [11] or albuminuria [12] with accuracy superior to conventional predictors.

Because CKD is a forerunner of heart failure and because heart failure leads to prerenal dysfunction [13,14], we also assessed to multidimensional classifiers associated with decreased left ventricular function. As published previously [15], HF1 combined information from 85 peptide fragments identified in 19 patients with diastolic left ventricular dysfunction and 19 controls. To generate the HF2 classifier, all urinary proteomic datasets from cases available in the Mosaiques database [9] were combined and compared with data from sex- and age-matched controls. Cases were 98 patients with left ventricular diastolic dysfunction recruited from our population [15] (n = 35) or admitted to the hospital because of overt heart failure (n = 63). The patients with overt heart failure were all on multiple drugs, included

49.2% women. Mean age was 67.1 years. The underlying cause of heart failure was ischemic cardiomyopathy (50.8%), dilated cardiomyopathy (28.6%), hypertrophic cardiomyopathy (1.6%), valvular heart disease (1.6%) or unspecified (17.4%). Comparing cases with controls identified 710 potential biomarkers, based on a P-value of less than 0.05 with adjustment for multiple testing applied. Using a take-one-out procedure [16] to remove potential biomarkers that are of no apparent value, the number of biomarkers was reduced to 671. A MosaiquesVisu software based classifier including these 671 urinary peptides was developed, using all 196 (98 cases and 98 controls) datasets. Full information of the polypeptides making up the HF1 and HF2 classifiers (Tables S1 and S2) and on the polypeptides with known amino-acid sequence (Tables S3 and S4) is available in the supplementary data.

Identification of covariables of the renal function indices

As shown in Table S6, serum creatinine increased with age (r^2 = 0.014), mean arterial pressure (r^2 = 0.005), the total-to-HDL serum cholesterol ratio (r^2 = 0.017), urinary albuminuria (r^2 = 0.021), and use of diuretics (r^2 = 0.033). In contrast, serum creatinine was lower in women than men (r^2 = 0.19), in smokers compared with non-smokers (r^2 = 0.007), and decreased with central obesity (r^2 = 0.005) and use of vasodilators (r^2 = 0.008). The coefficient of multiple determination (R^2) was 0.347.

eGFR calculated by the MDRD formula [17] (Table S6), was higher in smokers than non-smokers (r^2 = 0.005) and increased with γ-glutamyltransferase (r^2 = 0.005). eGFR based on the MDRD formula decreased with mean arterial pressure (r^2 = 0.035), the total-to-HDL serum cholesterol ratio (r^2 = 0.008), urinary albuminuria (r^2 = 0.018), and use of diuretics (r^2 = 0.022) and inhibitors of the renin system (r^2 = 0.009). R^2 was 0.146. Findings for the eGFR calculated according to the CKD-EPI formula ([18]) were similar. R^2 was 0.224.

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Table S1. List of 85 polypeptides included in the HF1 biomarker

Polypeptide			Cases		Controls			
ID	Mass (Da)	CE Time (min)	%	MA	%	MA	R	P-value (Unadjusted)
81272	2211.98	33.23	0	0	0.42	2.67	0	1.99E-03
129821	3333.36	19.42	0	0	0.47	2.39	0	8.72E-04
8725	949.4	25.79	0.05	1.94	0.63	2.28	0.067	2.22E-04
123106	3130.43	30.82	0.05	1.98	0.47	2.63	0.080	2.57E-03
1577	840.41	23.17	0.05	1.65	0.47	1.85	0.095	3.29E-03
103493	2658.22	19.5	0.05	3.36	0.47	3.29	0.109	4.71E-03
44146	1518.6	19.37	0.11	1.91	0.58	2.49	0.145	1.33E-03
4845	900.27	43.66	0.16	1.55	0.63	2.44	0.161	1.33E-03
37610	1421.59	38.71	0.11	1.73	0.53	1.87	0.192	6.07E-03
83441	2248.97	33.69	0.11	3.45	0.53	3.56	0.201	4.88E-03
74703	2087.84	19.42	0.11	2.64	0.53	2.7	0.203	6.76E-03
101157	2616.16	28.39	0.11	1.97	0.53	1.98	0.206	6.76E-03
103022	2649.2	34.85	0.16	2.52	0.68	2.56	0.232	2.50E-03
57360	1734.66	19.9	0.16	2.2	0.58	2.24	0.271	1.03E-02
46091	1554.66	28.59	0.16	2.08	0.53	2.24	0.280	1.18E-02
32022	1319.58	20.89	0.21	1.99	0.58	2.21	0.326	1.57E-02
102269	2638.18	28.42	0.26	2.3	0.68	2.49	0.353	1.26E-02
82708	2235.04	34.17	0.32	2.57	0.84	2.68	0.365	2.53E-03
188895	11967.55	20.47	0.26	2.68	0.63	2.94	0.376	9.50E-03
98089	2559.18	19.41	0.32	2.97	0.84	3	0.377	3.76E-03
138143	3593.47	20.2	0.26	2.67	0.68	2.68	0.381	1.50E-02
167786	4771.07	20.2	0.37	2.74	0.79	3.13	0.410	4.34E-03
61984	1835.71	19.91	0.53	2.64	1	3.12	0.448	1.33E-04
46369	1560.7	29.79	0.32	2.78	0.68	2.84	0.461	2.27E-02
143947	3801.77	33.46	0.37	2.26	0.79	2.24	0.473	2.67E-02
39275	1445.62	37.36	0.47	2.59	0.79	2.96	0.521	4.87E-03
56493	1716.66	20.18	0.47	2.56	0.79	2.74	0.556	2.11E-02
41972	1478.61	39.3	0.53	2.75	0.84	2.95	0.588	3.16E-03
24168	1195.48	37.51	0.58	2.8	0.84	3.26	0.593	3.12E-03
107858	2751.34	29.23	0.63	2.36	0.89	2.69	0.621	3.00E-03
23356	1179.52	37.49	0.58	2.63	0.84	2.9	0.626	2.67E-02
97599	2547.99	21.44	0.58	2.59	0.89	2.66	0.635	3.15E-02
8695	949.22	34.33	0.53	2.46	0.68	3.01	0.637	2.78E-02

Polypeptide			Cases		Controls			
ID	Mass (Da)	CE Time (min)	%	MA	%	MA	R	P-value (Unadjusted)
23697	1186.53	22.39	0.68	2.8	1	2.88	0.661	2.08E-02
36566	1401.38	36.56	0.58	2.77	0.74	3.27	0.664	8.74E-03
153832	4196.75	20.84	0.68	2.41	0.95	2.59	0.666	4.93E-03
26670	1235.56	26.65	0.63	3.02	0.84	3.3	0.686	1.08E-02
58050	1749.81	30.61	0.63	2.57	0.84	2.79	0.691	3.04E-02
28005	1255.48	35.77	0.68	3.08	0.84	3.4	0.733	3.19E-02
159396	4409.89	20	0.74	2.72	0.84	3.23	0.742	2.68E-02
69979	1996.79	20.98	0.79	2.86	0.95	3.17	0.750	8.53E-03
40737	1462.62	39.42	0.84	3.33	1	3.68	0.760	2.62E-04
65368	1901.82	43.83	0.79	3.17	0.89	3.61	0.779	1.52E-02
128086	3286.55	30.92	0.79	3.13	0.89	3.51	0.792	6.91E-04
73434	2067.82	20.62	0.84	3.1	1	3.28	0.794	1.42E-02
148086	3986.65	20.6	0.84	3.53	0.95	3.82	0.817	2.75E-03
108574	2764.21	42.63	0.79	3.56	0.89	3.85	0.821	2.43E-02
90344	2377.1	20.8	0.89	3.12	0.95	3.46	0.845	1.95E-02
36759	1405.61	39.04	0.89	2.94	0.95	3.18	0.866	1.02E-02
147541	3968.6	21.09	0.89	3.14	0.89	3.57	0.880	1.77E-03
28561	1265.59	27.09	0.89	3.36	0.89	3.79	0.887	1.10E-02
107460	2742.25	28.98	0.95	2.91	1	3.11	0.889	1.19E-02
32171	1321.59	28.37	0.95	4.07	1	4.27	0.906	1.82E-02
39322	1446.64	39.43	1	3.2	1	3.49	0.917	3.19E-02
35339	1378.61	28.82	1	3.36	1	3.53	0.952	1.54E-02
81196	2210.95	33.61	1	3.72	1	3.59	1.036	2.15E-02
41601	1469.67	23.69	1	3.72	1	3.56	1.045	2.33E-02
62866	1854.81	40.92	1	3.89	1	3.71	1.048	1.98E-02
99021	2570.19	42.56	1	3.88	1	3.7	1.049	1.19E-02
79136	2175	33.28	1	3.74	1	3.49	1.072	1.09E-02
50840	1623.73	24.12	0.95	4.17	0.95	3.86	1.080	9.77E-03
72533	2046.92	32.58	0.95	3.49	0.95	3.21	1.087	1.06E-02
57537	1737.78	23.73	1	4.02	0.95	3.82	1.108	2.15E-02
50212	1613.82	23.99	0.89	2.7	0.89	2.43	1.111	3.30E-02
60149	1794.8	23.92	1	3.72	0.95	3.47	1.128	6.20E-03
103198	2654.19	23.92	0.89	2.94	0.89	2.47	1.190	5.52E-03
104786	2679.2	23.53	1	3.58	0.89	3.34	1.204	7.89E-03

Polypeptide			Cases		Controls			
ID	Mass (Da)	CE Time (min)	%	MA	%	MA	R	P-value (Unadjusted)
33135	1338.6	23.99	1	2.86	0.89	2.65	1.213	1.20E-02
73291	2064.92	24.46	0.84	2.75	0.79	2.37	1.234	3.25E-02
45021	1532.62	26.35	1	2.82	0.89	2.55	1.243	1.67E-02
99475	2577.25	24.67	0.95	2.78	0.89	2.38	1.247	6.05E-03
40294	1452.66	23.61	1	2.85	0.84	2.62	1.295	2.17E-03
35424	1380.64	23.83	0.95	2.79	0.79	2.56	1.311	7.17E-03
131294	3375.57	31.92	1	2.87	0.79	2.71	1.341	1.80E-02
111564	2841.26	24.54	0.89	3.21	0.79	2.67	1.354	4.98E-03
104195	2663.2	23.51	0.89	2.61	0.74	2.29	1.371	2.07E-02
28747	1268.57	27.25	1	3.44	0.74	3.32	1.400	1.01E-02
44802	1526.69	23.92	0.79	2.51	0.63	2.1	1.499	1.10E-02
113452	2889.35	24.08	0.89	2.47	0.58	2.29	1.655	7.34E-03
69681	1989.88	32.44	0.84	2.43	0.42	2.51	1.936	2.03E-02
55516	1696.72	23.95	0.79	2.54	0.42	2.39	1.999	1.59E-02
80360	2196.02	33.16	0.68	2.74	0.26	2.73	2.625	1.15E-02
82784	2236.98	27.14	0.63	2.28	0.21	2.31	2.961	1.29E-02
56806	1723.52	37.74	0.53	2.31	0.11	2.52	4.417	1.03E-02
129182	3320.51	24.25	0.47	2.07	0.05	2.1	9.266	4.71E-03

ID, polypeptide identifier (SQL number); %, percentage of samples, in which the polypeptide could be detected; MA, mean signal amplitude of the polypeptides. R was calculated as ∑ (ln signal amplitude x frequency/number of participants) in controls divided by ∑ (ln signal amplitude x frequency/number of participants) in cases. The polypeptides were ordered by ascending R.

Table S2. List of 671 polypeptides included in the HF2 biomarker

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
5675	911.43	25.88	0.29	266.81	0.85	709.73	0.38	0
17968	1099.49	28.24	0.62	310.36	0.91	888.01	0.35	8.88178E-16
14906	1050.48	26.92	0.37	238.08	0.82	738.97	0.32	1.9984E-15
73434	2067.82	20.62	0.51	1158.94	0.93	2053.5	0.56	1.4877E-14
78073	2156.97	22.22	0.45	904.53	0.88	1576.04	0.57	1.12577E-13
69979	1996.79	20.98	0.39	720.87	0.86	1396.18	0.52	1.46772E-13
23697	1186.53	22.39	0.45	536.63	0.89	884.15	0.61	7.46292E-13
2659	860.36	26.14	0.26	194.46	0.71	568.02	0.34	1.86806E-12
67263	1934.79	19.94	0.27	474.89	0.74	916.03	0.52	2.22089E-12
30575	1297.58	27.36	0.33	1425.18	0.85	1526.54	0.93	4.74443E-12
61984	1835.71	19.91	0.43	884.19	0.85	1510	0.59	9.06009E-12
72641	2048.93	24.46	0.98	4334.17	0.96	1332.88	3.25	9.11588E-12
28561	1265.59	27.09	0.49	2855.06	0.81	7418.24	0.38	1.11318E-11
11413	981.59	24.8	0.49	401.63	0.85	1006.41	0.40	1.70459E-11
49958	1608.73	30.93	0.34	578.89	0.85	739.65	0.78	2.41796E-11
7408	935.45	23.68	0.05	36.97	0.46	169.15	0.22	2.43741E-11
2505	858.39	23.24	0.34	191.41	0.76	383.25	0.50	4.6019E-11
23518	1182.55	28.27	0.12	62.68	0.55	136.09	0.46	4.82525E-11
35339	1378.61	28.82	0.95	2232.32	1	3398.04	0.66	4.97484E-11
72343	2042.07	25.14	0.43	10352.8	0.03	1273.44	8.13	6.103E-11
56493	1716.66	20.18	0.24	416.31	0.7	672.93	0.62	7.75853E-11
17694	1096.48	26.08	0.67	3573.1	0.94	5547.8	0.64	1.67514E-10
28466	1263.54	22.73	0.37	604.76	0.83	626.22	0.97	1.70054E-10
51916	1636.7	20.03	0.43	1031.8	0.84	1378.19	0.75	1.90195E-10
87692	2327.91	21	0.15	273.02	0.58	355.4	0.77	2.80282E-10
60352	1798.72	36.95	0.1	131.41	0.5	280.84	0.47	3.49119E-10
124909	3194.42	30.4	0.55	746	0.17	292.65	2.55	9.42768E-10
115312	2939.15	33.77	0.17	203.53	0.57	283.48	0.72	1.08754E-09
43543	1508.68	29.33	0.59	1979.23	0.93	2945.44	0.67	1.57317E-09
32470	1326.55	29.2	0.35	218.46	0.72	362.3	0.60	1.67426E-09
42404	1487.65	29.62	0.38	336.54	0.75	655.59	0.51	1.99523E-09
46184	1556.74	40.03	0.1	154.65	0.48	400.39	0.39	2.88512E-09

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
30699	1299.58	22.38	0.39	428.35	0.84	409.15	1.05	3.0367E-09
16773	1080.48	27.77	0.09	89	0.46	194.48	0.46	3.05367E-09
19828	1129.46	27.91	0.35	149.33	0.69	321.85	0.46	3.64891E-09
28132	1257.64	19.92	0.42	1104.88	0.06	529.33	2.09	5.52722E-09
84164	2257.87	35.93	0.18	437.59	0.57	1175.56	0.37	6.19304E-09
15216	1058.48	24.89	0.49	1000.53	0.13	477.43	2.10	6.55992E-09
147541	3968.6	21.09	0.63	1479.55	0.85	2807.96	0.53	7.13959E-09
13342	1016.45	25.79	0.87	866.5	0.97	1808.79	0.48	1.1465E-08
57531	1737.78	31	0.84	1573.88	0.94	2870.95	0.55	1.19037E-08
66161	1916.77	20.32	0.5	1353.17	0.82	2464.52	0.55	1.34118E-08
18943	1114.49	25.55	0.82	2185.57	0.93	4029.69	0.54	1.36723E-08
90840	2389.24	22.4	0.43	11705.46	0.08	506.56	23.11	1.48139E-08
33812	1352.56	29.77	0.23	217.57	0.63	234.65	0.93	1.71495E-08
85020	2276.02	27.23	0.46	2506.77	0.81	3634.07	0.69	1.72695E-08
48751	1592.7	22.18	0.37	1093.01	0.83	577.9	1.89	1.8047E-08
77763	2149.96	27.76	0.97	3399.7	0.98	1724.29	1.97	2.02281E-08
121716	3091.44	28.4	0.44	486.01	0.76	666.07	0.73	2.11918E-08
73291	2064.92	24.46	0.86	1417.64	0.73	416.98	3.40	2.43001E-08
41434	1466.65	28.52	0.35	426.47	0.72	472.77	0.90	2.62457E-08
63812	1874.83	30.82	0.08	197.69	0.43	200.85	0.98	2.67978E-08
97599	2547.99	21.44	0.38	405.88	0.72	558.72	0.73	2.69885E-08
64054	1878.79	20.72	0.39	773.63	0.81	677.75	1.14	2.89355E-08
125749	3223.31	21.61	0.18	290.75	0.55	402.35	0.72	3.91738E-08
34009	1354.61	35.71	0.34	334.66	0.03	308.86	1.08	5.4766E-08
138067	3590.7	29	0.07	114.33	0.4	279.39	0.41	5.60047E-08
60628	1806.83	23.06	0.34	361	0.78	295.44	1.22	6.03294E-08
15561	1065.5	25.45	0.04	61.89	0.34	164.52	0.38	6.25753E-08
99808	2584.23	35.18	0.67	449.89	0.9	700.47	0.64	6.39811E-08
82708	2235.04	34.17	0.5	396.97	0.78	760.84	0.52	7.40293E-08
31480	1312.55	29.77	0.89	1505.39	0.95	2228.44	0.68	1.04546E-07
107198	2736.4	21.3	0.31	15025.57	0.02	2343.04	6.41	1.08135E-07
123969	3158.44	29.71	0.86	1809.86	0.74	981.31	1.84	1.23125E-07
106195	2716.36	20.19	0.34	14019.79	0.04	718.01	19.53	1.2609E-07
57360	1734.66	19.9	0.1	227.95	0.44	329.02	0.69	1.29332E-07

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
25294	1215.43	27.59	0.1	295.73	0.42	748.62	0.40	1.33132E-07
61711	1828.85	21.2	0.56	877.35	0.28	212.55	4.13	1.3589E-07
19284	1121.49	27.68	0.05	270.31	0.35	255.97	1.06	1.36075E-07
63209	1860.83	21.4	0.44	1458.34	0.9	1119.04	1.30	1.36324E-07
56662	1720.69	19.67	0.11	193.27	0.44	352.82	0.55	1.59569E-07
107460	2742.25	28.98	0.86	919.94	0.96	1398.45	0.66	1.83175E-07
14478	1040.47	25.05	0.36	300.27	0.74	286.94	1.05	1.90817E-07
46338	1560.58	21.77	0.31	567.01	0.68	659.38	0.86	2.07678E-07
23409	1180.52	35.7	0.23	309.68	0.58	602.16	0.51	2.1728E-07
1577	840.41	23.17	0.15	107.18	0.5	205.69	0.52	2.38837E-07
88282	2339	34.01	0.56	594.88	0.84	846.66	0.70	3.18353E-07
118224	3013.29	22.29	0.64	4554.03	0.91	7727.54	0.59	3.19188E-07
58084	1750.78	23.83	0.58	950.75	0.9	1120.91	0.85	3.27827E-07
153832	4196.75	20.84	0.38	264.09	0.7	415	0.64	3.3455E-07
18988	1115.5	21.57	0.07	422.96	0.39	340.14	1.24	3.6776E-07
72533	2046.92	32.58	0.94	3157.59	0.91	1786.23	1.77	3.89387E-07
37340	1415.64	23.55	0.34	250.8	0.05	172.78	1.45	4.33972E-07
29685	1283.55	27.27	0.17	174.58	0.5	235.3	0.74	4.75252E-07
74703	2087.84	19.42	0.1	318.89	0.42	493.74	0.65	4.77952E-07
43863	1513.63	29.51	0.03	190.62	0.3	158.41	1.20	4.91617E-07
56884	1725.59	38.32	0.9	1923.19	1	3094.58	0.62	5.3905E-07
119660	3044.42	34.29	0.05	54.27	0.32	311.66	0.17	5.47446E-07
177848	6211.74	20.29	0.2	438.96	0.53	666.34	0.66	5.48173E-07
61221	1817.69	20.23	0.77	3207.87	0.97	4826.24	0.66	5.48282E-07
91342	2403.19	24.94	0.45	333.4	0.15	222.75	1.50	5.57645E-07
64170	1880.9	43.91	0.3	476.28	0.6	1066.06	0.45	5.73076E-07
104954	2682.14	22.49	0.81	926.16	0.99	1228.01	0.75	5.88132E-07
70485	2009.88	32.29	0.77	801.64	0.55	434.86	1.84	5.98055E-07
90344	2377.1	20.8	0.68	1380.11	0.93	2542.67	0.54	6.43034E-07
73015	2059	33.08	0.51	433.53	0.23	90.09	4.81	6.5827E-07
89083	2352.05	26.75	0.6	768.28	0.34	266.61	2.88	6.84124E-07
20862	1143.52	36.97	0.31	168.72	0.6	380.82	0.44	7.42932E-07
50904	1624.55	37.73	0.86	1193.34	0.99	1743.58	0.68	7.47011E-07
76636	2124.84	20.37	0.07	212.77	0.36	248.44	0.86	7.89066E-07

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
156081	4289.93	28.78	0.46	2355	0.74	3896.07	0.60	8.44141E-07
80306	2194.97	20.17	0.17	374.8	0.5	495.49	0.76	8.77308E-07
36769	1405.64	20.14	0.19	290.39	0.52	365.14	0.80	9.33202E-07
8503	947.47	24.74	0.19	140.61	0.48	327.52	0.43	9.48105E-07
99475	2577.25	24.67	0.87	691.24	0.9	332.35	2.08	9.55869E-07
89900	2368.04	26.75	0.65	507.61	0.45	162.4	3.13	9.71083E-07
73913	2076.95	21.78	0.27	649.6	0.6	1056.5	0.61	1.02976E-06
80829	2203.64	35.26	0.04	61.06	0.3	110.5	0.55	1.09123E-06
148557	4002.62	20.66	0.36	655.77	0.65	1304.21	0.50	1.09596E-06
87365	2320.07	20.73	0.09	185.88	0.39	263.28	0.71	1.25682E-06
49948	1608.68	22.35	0.3	427.86	0.73	248.88	1.72	1.28713E-06
104786	2679.2	23.53	0.97	3608.38	0.91	2259.68	1.60	1.35314E-06
144635	3831.81	28.48	0.33	585.57	0.66	1075.25	0.54	1.46424E-06
129821	3333.36	19.42	0.05	497.52	0.33	265.9	1.87	1.56159E-06
33973	1353.66	25.63	0.68	312.44	0.89	463.05	0.67	1.57151E-06
116812	2977.18	19.52	0.35	759.33	0.72	687.85	1.10	1.67034E-06
67632	1943.01	24.94	0.32	13045.5	0.05	4808.08	2.71	1.69836E-06
101839	2628.22	34.97	0.86	1078.45	0.73	573.03	1.88	0.000001759
110913	2823.33	29.12	0.5	386.13	0.75	629.26	0.61	1.82329E-06
114702	2923.43	36.92	0.26	171.24	0.57	254.69	0.67	1.92617E-06
23724	1187.36	35.69	0.48	1351.07	0.82	1360.67	0.99	1.92706E-06
22725	1171.51	29.18	0.17	65.32	0.46	149.11	0.44	1.92858E-06
101157	2616.16	28.39	0.09	120.1	0.4	95.3	1.26	1.94913E-06
134635	3478.43	41.74	0.23	498.11	0.52	828.56	0.60	1.9993E-06
32823	1332.54	21.74	0.43	1306.32	0.15	574.88	2.27	2.04622E-06
124193	3166.27	22.06	0.44	674.01	0.71	1136.6	0.59	2.13141E-06
17045	1085.42	20.77	0.1	333.94	0.38	1369.33	0.24	2.1539E-06
60751	1807.81	20.65	0.86	2286.7	0.97	3288.38	0.70	2.19769E-06
120423	3064.32	20.57	0.28	453.18	0.56	815	0.56	2.21835E-06
42378	1486.68	21.15	0.37	317.84	0.7	433.68	0.73	2.27212E-06
118597	3021.35	23.42	0.78	1741.99	0.95	2083.36	0.84	2.82992E-06
55143	1692.8	30.89	0.43	586.61	0.7	907.46	0.65	2.93441E-06
150781	4078.81	33.14	0.61	430.13	0.41	153.97	2.79	3.00875E-06
44146	1518.6	19.37	0.16	301.07	0.47	429.11	0.70	3.0478E-06

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
16059	1071.49	21.43	0.24	168.13	0.56	171.56	0.98	3.0793E-06
64431	1885.65	38.82	0.31	305.69	0.69	250.54	1.22	3.12346E-06
70456	2008.9	32.29	0.16	498.15	0.47	654.13	0.76	3.33657E-06
73010	2058.94	23.15	0.4	284.87	0.71	324.45	0.88	3.4391E-06
71943	2034.88	19.52	0.09	178.68	0.36	388.45	0.46	3.45045E-06
67723	1945.88	41.9	0.33	815.93	0.07	219.59	3.72	3.66996E-06
44679	1524.65	20.03	0.58	696.74	0.9	822.72	0.85	3.71683E-06
12998	1009.45	27.27	0.14	130.04	0.44	195.64	0.66	3.82016E-06
38011	1426.64	22.42	0.09	184.4	0.36	193.02	0.96	3.94795E-06
38586	1435.51	19.75	0.08	157.25	0.34	273.26	0.58	3.96342E-06
122400	3108.45	31.28	0.64	266.08	0.86	354.59	0.75	4.06715E-06
24660	1203.57	26.76	0.13	77.91	0.41	159.05	0.49	4.17671E-06
58880	1764.68	19.91	0.23	354.57	0.54	558.35	0.64	4.46484E-06
105352	2695.2	23.52	0.97	5094.04	0.96	3271.88	1.56	4.55032E-06
77018	2133.96	27.77	0.96	5570.45	0.95	2768.02	2.01	4.8937E-06
128435	3295.53	25.45	0.24	163.97	0.53	343.3	0.48	5.13197E-06
13145	1012.5	35.03	0.12	66.64	0.39	161.15	0.41	5.30167E-06
132057	3401.66	23.49	0.4	866.82	0.67	1219.88	0.71	5.4511E-06
52769	1649.73	22.64	0.7	886.2	0.88	1103.43	0.80	5.64197E-06
122216	3106.19	19.58	0.08	400.63	0.36	297.86	1.35	5.81026E-06
23224	1178.39	20.71	0.26	428.98	0.56	423.64	1.01	5.93879E-06
137922	3583.64	41.47	0.23	423.34	0.56	527.89	0.80	6.2693E-06
98596	2563.15	21.21	0.64	1170.12	0.89	1512.92	0.77	6.29775E-06
74187	2080.94	20.2	0.42	809.32	0.71	1202.1	0.67	6.65843E-06
58050	1749.81	30.61	0.45	409.94	0.74	505.2	0.81	7.01523E-06
19773	1128.39	33.59	0.78	1391.02	0.83	2748.43	0.51	7.33822E-06
38780	1438.66	30.2	0.21	431.04	0.54	421.44	1.02	7.56112E-06
46091	1554.66	28.59	0.18	150.82	0.51	126.48	1.19	7.81906E-06
148717	4008.81	23.42	0.4	9006.94	0.13	272.16	33.09	7.91402E-06
80012	2191.99	22.39	0.45	641.13	0.74	794.69	0.81	8.44825E-06
150441	4062.8	33.14	0.6	774.68	0.43	260.94	2.97	8.47916E-06
158341	4368.9	20.21	0.24	1384.93	0.56	1531.99	0.90	8.97593E-06
59773	1783.79	39.82	0.33	291.61	0.63	356.09	0.82	9.16298E-06
59295	1773.82	34.6	0.31	111.58	0.6	184.11	0.61	9.19093E-06

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
72896	2055.94	25.44	0.92	1350.02	0.96	814.06	1.66	9.81315E-06
143652	3788.82	25.19	0.22	163.71	0.52	248.58	0.66	1.00722E-05
49243	1593.69	22.38	0.16	573.04	0.48	278.35	2.06	1.01356E-05
141007	3696.76	26.94	0.11	184.21	0.39	260.09	0.71	1.0196E-05
151244	4097.87	24.61	0.62	747.28	0.81	1311.78	0.57	1.02206E-05
65593	1907.77	23.78	0.1	98.62	0.38	109.12	0.90	1.08821E-05
134053	3462.35	19.37	0.1	383.4	0.38	415.89	0.92	1.08821E-05
56514	1716.77	28	0.62	473.76	0.88	667.19	0.71	1.16213E-05
76090	2109.96	21.09	0.12	177.85	0.41	166.73	1.07	1.19602E-05
39064	1442.63	27.63	0.55	530.59	0.32	213.77	2.48	1.19912E-05
155132	4251.98	28.77	0.53	337.4	0.69	749.7	0.45	1.21296E-05
117823	3002.24	23.8	0.19	130.66	0.51	115.1	1.14	1.27561E-05
35204	1375.6	23.25	0.23	206.36	0.57	182.85	1.13	1.29376E-05
91542	2407.09	27.67	0.68	463.41	0.92	572.79	0.81	1.36818E-05
36868	1407.66	37.23	0.34	201.51	0.6	348.48	0.58	1.38609E-05
125103	3202.43	30.6	0.16	159.05	0.44	208.66	0.76	1.392E-05
42866	1496.68	30.37	0.23	299.77	0.57	229.35	1.31	1.41857E-05
14047	1032.45	25.9	0.44	136.42	0.66	268.23	0.51	1.43904E-05
37903	1424.66	39.3	0.86	1563.29	0.98	2260.54	0.69	1.49198E-05
49122	1592.73	19.52	0.27	334.6	0.57	437.92	0.76	1.59179E-05
63135	1859.8	31.39	0.18	299.62	0.47	403	0.74	1.64336E-05
53744	1666.78	30.66	0.33	264.94	0.63	258.89	1.02	1.66223E-05
12993	1009.41	20.98	0.08	77.54	0.32	108.42	0.72	1.86629E-05
38798	1438.67	27.88	0.88	3752.67	1	4550.73	0.82	1.88571E-05
99919	2587.2	21.1	0.18	468.84	0.47	666.66	0.70	1.96726E-05
51838	1635.65	37.38	0.1	226.47	0.35	427.2	0.53	1.98042E-05
71490	2029.85	20.39	0.31	445.78	0.67	335.8	1.33	2.06707E-05
43605	1509.79	29.5	0.5	7057.59	0.2	6131.35	1.15	2.10746E-05
55314	1693.76	20.51	0.27	348.39	0.58	262.53	1.33	2.13348E-05
111426	2837.36	23.87	0.55	4883.89	0.25	3574.86	1.37	2.16434E-05
71602	2030.93	32.61	0.91	1846.54	0.91	1008.41	1.83	2.23965E-05
51175	1630.74	20.65	0.18	210.58	0.46	273.82	0.77	2.34887E-05
26163	1226.53	21.02	0.58	673.84	0.83	758.01	0.89	2.51304E-05
12434	995.39	25.11	0.5	284.67	0.23	132.3	2.15	2.56872E-05

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
68411	1962.83	21.97	0.23	533.25	0.56	394.1	1.35	3.01098E-05
55917	1703.84	33.58	0.23	298.07	0.51	743.94	0.40	3.01684E-05
67306	1935.81	20.66	0.23	406.53	0.53	416.67	0.98	3.02761E-05
42188	1483.66	22.59	0.11	642.28	0.36	785.06	0.82	3.03571E-05
156445	4305.94	28.83	0.86	1787.33	0.96	2673.53	0.67	3.0913E-05
123634	3148.28	24.16	0.34	301.7	0.64	284.93	1.06	3.383E-05
98891	2567.13	34.8	0.71	265.4	0.54	135.09	1.96	3.73327E-05
76053	2108.93	32.93	0.07	108.86	0.3	138.9	0.78	3.80922E-05
50638	1620.7	22.66	0.31	522.57	0.6	477.87	1.09	3.93812E-05
75846	2103.96	33.04	0.97	2774.85	0.98	1843.41	1.51	4.15814E-05
56139	1708.79	30.59	0.71	818.24	0.89	1465.01	0.56	4.27471E-05
23423	1180.54	25.62	0.08	194.2	0.31	98.15	1.98	4.48896E-05
32336	1324.57	21.27	0.13	338.38	0.39	354.8	0.95	4.59736E-05
16976	1084.43	25.23	0.92	1900.2	0.95	2435.82	0.78	4.63093E-05
43851	1513.44	36.79	0.17	643.87	0.47	495.42	1.30	4.64513E-05
24958	1209.53	26.15	0.43	509.5	0.69	602.63	0.85	4.64642E-05
62323	1842.85	24.07	0.1	487.41	0.34	1767.57	0.28	4.65518E-05
61576	1825.8	31.93	0.32	298.73	0.61	357.37	0.84	5.08976E-05
93227	2442.07	34.1	0.79	708.3	0.94	855.09	0.83	5.46349E-05
1495	838.4	35.06	0.16	17.46	0.36	376.78	0.05	5.78108E-05
38910	1440.56	24.3	0.3	613.88	0.63	406.33	1.51	5.98345E-05
60248	1796.77	30.92	0.24	243.77	0.52	219.24	1.11	6.25281E-05
184099	8853.77	21.1	0.15	1491.8	0.42	1670.55	0.89	6.42389E-05
130044	3336.5	39.38	0.18	1540.1	0.45	1948.69	0.79	6.59767E-05
102819	2644.22	21.15	0.3	448.42	0.54	706.56	0.63	6.6046E-05
61405	1821.81	30.17	0.34	460.77	0.63	562.02	0.82	6.71091E-05
26412	1231.42	21.51	0.14	561.76	0.4	499.34	1.13	6.86967E-05
108724	2767.32	21.67	0.29	183.13	0.51	322.27	0.57	6.92951E-05
105105	2687.22	28.99	0.13	64.83	0.36	112.37	0.58	7.16723E-05
103224	2655.14	22.33	0.15	130.88	0.42	129.08	1.01	7.35479E-05
106678	2726.25	28.92	0.23	195.1	0.48	200.14	0.97	7.37277E-05
121940	3098.44	30.06	0.71	485.63	0.89	725.01	0.67	7.37948E-05
23628	1184.56	26.4	0.18	151.25	0.45	146.39	1.03	7.51756E-05
115050	2932.32	34.15	0.36	381.56	0.68	305.41	1.25	8.26656E-05

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
125799	3223.42	39.13	0.64	2096.08	0.86	2280.85	0.92	8.30968E-05
32171	1321.59	28.37	0.97	8865.26	0.96	18773.43	0.47	8.59358E-05
40091	1449.64	21.86	0.95	5489.33	0.99	7666.71	0.72	8.73287E-05
130077	3337.45	22.81	0.21	466	0.45	762.99	0.61	8.80379E-05
49713	1604.73	30.34	0.11	310.87	0.36	186.14	1.67	9.22588E-05
81457	2216.03	33.83	0.55	216.02	0.73	376.59	0.57	9.53148E-05
3743	883.41	23.26	0.21	97.1	0.47	132.98	0.73	9.79105E-05
11282	980.5	22.41	0.26	80.98	0.48	123	0.66	9.83538E-05
92231	2421	34.86	0.18	115.14	0.44	157.74	0.73	9.88539E-05
143947	3801.77	33.46	0.43	201.71	0.66	318.74	0.63	9.93604E-05
52730	1649.71	19.58	0.15	181.54	0.38	316.61	0.57	0.000109001
62547	1847.89	43.67	0.15	144.9	0.38	350.11	0.41	0.000109001
40487	1457.6	21.93	0.16	393.55	0.44	238.34	1.65	0.000114019
61304	1818.83	30.95	0.63	3412.56	0.53	646.82	5.28	0.000114375
45243	1535.68	22	0.13	725.47	0.4	474.07	1.53	0.000116626
44464	1521.69	30.53	0.27	156.32	0.54	191.66	0.82	0.000117125
159259	4404.84	20.67	0.48	803.14	0.7	1234.67	0.65	0.000122825
98485	2560.12	34.15	0.23	138.35	0.52	111.61	1.24	0.00012327
62000	1835.84	24.04	0.55	464.05	0.33	226.66	2.05	0.000123449
48394	1583.7	23.27	0.51	561.63	0.79	543.66	1.03	0.000128732
82026	2226.99	26.28	0.6	13874.99	0.85	17489.37	0.79	0.000133192
126982	3256.53	33.03	0.38	1063.61	0.63	1434.24	0.74	0.000135924
58941	1765.81	31	0.7	1567.7	0.84	2259.23	0.69	0.000138958
121070	3076.23	19.58	0.45	1096.34	0.75	1084.22	1.01	0.000140442
111304	2834.19	22.47	0.23	329.83	0.51	199.7	1.65	0.000141054
71312	2025.87	32.23	0.94	1078.97	0.92	674.42	1.60	0.00014927
150139	4059.65	20.45	0.13	507.21	0.38	588.82	0.86	0.000159992
63098	1858.84	24.26	0.19	568.26	0.43	959.79	0.59	0.00016324
125263	3205.27	19.66	0.67	1121.53	0.84	1531.51	0.73	0.000165029
37949	1425.59	22.32	0.84	4007.86	0.98	4332.71	0.93	0.000170035
74987	2089.96	39.52	0.34	200.94	0.57	226.12	0.89	0.000177515
102725	2642.21	27.7	0.73	374.49	0.88	483.16	0.78	0.000179073
142080	3734.72	32.5	0.68	213.49	0.77	453.29	0.47	0.000180004
28850	1270.55	29.38	0.15	159.62	0.39	185.38	0.86	0.000181889

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
57265	1732.77	28.18	0.8	2318.48	0.93	3123.31	0.74	0.000181905
88093	2336.04	26.66	0.43	261.05	0.21	89.41	2.92	0.000192814
32022	1319.58	20.89	0.16	208.23	0.41	233.67	0.89	0.000196668
48580	1588.71	30.15	0.57	657.3	0.79	972.89	0.68	0.000197355
17830	1097.5	25.41	0.39	352.81	0.17	185.34	1.90	0.000198331
156878	4321.94	25.2	0.33	3184.53	0.11	966.74	3.29	0.000204459
23968	1191.52	36.18	0.23	206.01	0.46	401.04	0.51	0.000207062
68663	1968.88	25.2	0.47	519.19	0.21	557.78	0.93	0.000210243
181250	7958.47	34.39	0.14	419.43	0.38	412.05	1.02	0.000211993
106067	2713.23	29.22	0.22	134.31	0.48	149.06	0.90	0.00023196
117317	2987.35	38.55	0.56	910.56	0.35	295.25	3.08	0.00023425
136697	3556.59	23.95	0.54	822.31	0.75	1181.43	0.70	0.000239633
61573	1825.79	20.14	0.73	2839.49	0.94	3352.31	0.85	0.000258194
124886	3193.38	22.64	0.46	1372.7	0.74	1238.23	1.11	0.000262225
20700	1140.52	25.38	0.22	147.49	0.46	213.25	0.69	0.000263445
61340	1819.83	32.13	0.32	839.62	0.13	71.66	11.72	0.000273104
43226	1503.66	29.68	0.11	90.04	0.31	207.6	0.43	0.000277879
138143	3593.47	20.2	0.26	536.52	0.52	641.81	0.84	0.000278071
124735	3187.36	35.62	0.32	284.01	0.53	347.81	0.82	0.000281837
173077	5213.09	22.43	0.39	329.27	0.67	257.5	1.28	0.000283464
108021	2754.27	29.68	0.67	306.74	0.79	450.84	0.68	0.000283697
26670	1235.56	26.65	0.5	849.6	0.57	2832.67	0.30	0.000300503
100020	2589.06	22.56	0.19	139.26	0.43	159.63	0.87	0.000305354
159396	4409.89	20	0.48	1279.87	0.72	1793.86	0.71	0.000312092
49295	1594.73	23.05	0.81	711.82	0.81	330.8	2.15	0.000312635
65312	1900.87	32	0.18	204.42	0.43	186.61	1.10	0.000324669
118163	3011.39	29.75	0.89	1143.92	0.94	1539.79	0.74	0.000329751
97349	2541.19	27.89	0.13	208.47	0.36	112.03	1.86	0.000340482
31275	1310.59	21.39	0.11	148.01	0.33	121.11	1.22	0.000353299
139554	3632.74	33.23	0.12	117.32	0.33	129.73	0.90	0.000357574
65035	1895.07	21.4	0.44	916.62	0.21	565.49	1.62	0.000364447
148086	3986.65	20.6	0.81	3872.36	0.91	5676.99	0.68	0.000392643
141672	3718.72	32.48	0.79	334.28	0.81	662.54	0.50	0.000400146
42594	1491.74	39.83	0.55	381.96	0.71	561.66	0.68	0.000411414

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
72048	2034.99	40.19	0.31	104.8	0.52	148.21	0.71	0.000432848
123287	3137.41	30.35	0.7	506.04	0.6	342.26	1.48	0.000436572
44633	1523.84	29.75	0.36	1404.38	0.63	2092.26	0.67	0.00044567
3052	868.41	23.31	0.4	84.26	0.57	230.43	0.37	0.000452634
103022	2649.2	34.85	0.14	617.79	0.39	354.22	1.74	0.000454412
86226	2302.9	43.13	0.31	373.04	0.11	124.32	3.00	0.000460882
14751	1046.43	27.64	0.17	70.73	0.4	79.7	0.89	0.000468596
20896	1144.36	35.49	0.11	96.37	0.3	183.47	0.53	0.000487667
47855	1576.74	19.51	0.43	527.24	0.66	750.62	0.70	0.000490581
50840	1623.73	24.12	0.89	9939.06	0.99	5733.56	1.73	0.000494355
175343	5574.25	23.2	0.56	1200.44	0.89	859.43	1.40	0.000505923
105661	2702.21	38.08	0.7	704.9	0.52	352.49	2.00	0.000512809
86951	2314.01	33.66	0.58	599.79	0.8	629.88	0.95	0.000518205
139064	3616.72	33.19	0.57	285.22	0.7	423.62	0.67	0.000523514
55582	1697.74	30.88	0.87	1006.3	0.94	1338.55	0.75	0.000533651
136698	3556.6	22.64	0.35	6465.83	0.15	1524.74	4.24	0.00054874
184206	8917.25	22.55	0.34	452.04	0.61	435.05	1.04	0.00057263
5661	911.26	34.35	0.89	788.53	0.89	2126.53	0.37	0.000576545
4976	902.41	20.85	0.76	514.64	0.9	730.44	0.70	0.000581238
121775	3092.46	31.25	0.64	333.92	0.76	477.73	0.70	0.000581421
52189	1640.58	23.24	0.87	5589.55	0.98	7511.1	0.74	0.000588492
7953	940.44	25.14	0.35	128.44	0.15	60.45	2.12	0.000591455
61945	1834.82	31.09	0.78	6969.39	0.77	1660.16	4.20	0.000596655
62080	1837.8	30.56	0.14	1953.08	0.35	330.34	5.91	0.000598868
86677	2308.02	27.34	0.33	200.55	0.56	221.45	0.91	0.000606509
101786	2627.23	34.99	0.14	527.11	0.39	308.13	1.71	0.000610272
22835	1173.53	37.49	0.26	186.97	0.46	281.09	0.67	0.000632983
44592	1523.67	21.97	0.81	6161.47	0.85	7615.86	0.81	0.000640669
149142	4025.6	20.78	0.24	245.17	0.45	476.52	0.51	0.000652689
107858	2751.34	29.23	0.48	313.21	0.67	439.04	0.71	0.000653069
14763	1046.51	25.35	0.13	1498.96	0.34	336.22	4.46	0.000659461
66197	1916.95	34.19	0.35	161.44	0.6	147.17	1.10	0.000663718
19655	1126.51	25.52	0.41	152.24	0.16	224.59	0.68	0.000669938
102371	2639.29	21.42	0.33	297.28	0.54	384.8	0.77	0.000678342

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
79918	2190.99	25.82	0.38	1497.08	0.17	1238.23	1.21	0.000689704
61332	1819.8	23.36	0.95	5644.1	0.99	6228.52	0.91	0.000695456
65257	1899.85	24.83	0.43	230.8	0.26	91.2	2.53	0.00069733
143333	3774.72	22.94	0.36	4239.56	0.18	298.21	14.22	0.000710839
18833	1113.46	27.3	0.61	285.45	0.73	404.95	0.70	0.00071897
145479	3871.79	27.57	0.3	292.99	0.56	288.03	1.02	0.000724096
96716	2525.2	27.74	0.49	548.94	0.63	841.82	0.65	0.000726318
20659	1139.49	20.97	0.33	1024.77	0.55	1503.22	0.68	0.000733567
24510	1200.54	24.14	0.55	3745.12	0.66	7839.78	0.48	0.000753934
25295	1215.45	26.88	0.21	642.19	0.43	956.98	0.67	0.000764996
56992	1728.77	36.77	0.41	295.3	0.66	266.8	1.11	0.000768981
117524	2994.38	29.6	0.17	105.93	0.36	207.33	0.51	0.000781908
89642	2361.11	20.79	0.3	279.82	0.48	531.27	0.53	0.000785407
92029	2414.63	35.62	0.77	757.09	0.56	584.48	1.30	0.000796642
58633	1761.69	19.37	0.12	222.09	0.32	280.46	0.79	0.00081529
16779	1080.5	25.69	0.17	206.52	0.39	191.34	1.08	0.000835479
85076	2277.01	27.22	0.6	2154.86	0.44	1128.52	1.91	0.000857711
27350	1247.52	22	0.79	1332.67	0.98	1454.94	0.92	0.000880047
28669	1267.54	21.17	0.15	374.32	0.38	275.42	1.36	0.000885422
15296	1060.38	38.31	0.31	85.06	0.51	154.13	0.55	0.000895912
57537	1737.78	23.73	0.91	5998.4	0.99	5980.02	1.00	0.000900403
33938	1353.59	21.48	0.68	690.47	0.56	373.67	1.85	0.000913542
43828	1512.69	26.62	0.45	198.48	0.26	115.21	1.72	0.000944663
97736	2551.15	34.72	0.67	646.04	0.57	205.4	3.15	0.000966464
21641	1155.49	20.85	0.28	262.3	0.51	268.38	0.98	0.001006469
92871	2430.59	35.54	0.73	1003.39	0.51	942.45	1.06	0.00101272
99251	2574.01	32.81	0.19	86.81	0.42	82.91	1.05	0.001012725
58355	1754.9	31.26	0.76	6326.81	0.88	8174.64	0.77	0.001027498
128650	3302.59	23.29	0.34	214.12	0.58	195.96	1.09	0.001058052
147376	3959.69	19.9	0.19	615.55	0.42	841.72	0.73	0.001070683
12264	992.42	20.4	0.19	132.87	0.41	132.73	1.00	0.001077376
92410	2423.09	27.67	0.62	250.12	0.83	286.44	0.87	0.001085023
29823	1286.42	36.41	0.15	95.57	0.35	99.79	0.96	0.001092108
146964	3944.71	24.55	0.29	227.59	0.5	248.84	0.91	0.001132718

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
34267	1359.61	23.19	0.19	246.89	0.44	162.86	1.52	0.001150035
67951	1950.85	35.77	0.78	595.93	0.88	751.65	0.79	0.001167898
167786	4771.07	20.2	0.4	1011.51	0.6	1341.6	0.75	0.001201307
33209	1339.6	27.49	0.45	180.64	0.65	214.9	0.84	0.001204047
20204	1137.51	26.43	0.11	434.52	0.3	150.29	2.89	0.001219826
112106	2854.36	34.86	0.94	3427.59	1	4566.21	0.75	0.001220385
121989	3100.42	29.96	0.46	549.99	0.25	439.19	1.25	0.001230127
97965	2557.17	28.25	0.29	185.08	0.51	152.9	1.21	0.001254961
84484	2264.94	43.29	0.35	226.09	0.15	173.73	1.30	0.001284535
15887	1069.47	26.33	0.44	139.18	0.57	232.32	0.60	0.00128533
61404	1821.82	31.78	0.11	762.89	0.31	243.75	3.13	0.001300509
14071	1032.5	21.21	0.52	984.59	0.71	1197.89	0.82	0.001312967
21972	1160.36	35.6	0.89	1675.26	0.93	2434.96	0.69	0.001334528
68081	1954.01	32.41	0.11	823.79	0.32	172.68	4.77	0.00134757
152967	4169.93	33.58	0.82	824.03	0.85	1355.53	0.61	0.001360744
42776	1494.66	30.4	0.49	285.32	0.72	284.56	1.00	0.001361154
140112	3657.67	40.71	0.7	1392.88	0.83	1698.11	0.82	0.001409881
912	826.2	33.41	0.16	119	0.35	145.85	0.82	0.001462682
28385	1262.46	38.23	0.19	476.93	0.43	282.43	1.69	0.001474387
55315	1693.76	23.48	0.13	174.77	0.34	139.73	1.25	0.001475157
41665	1470.68	21.08	0.24	148.06	0.48	162.58	0.91	0.001507623
128525	3298.46	36.05	0.2	158.28	0.4	313.94	0.50	0.001557902
123750	3152.34	24.55	0.81	867.05	0.67	551.81	1.57	0.001574687
77236	2138.95	24.24	0.36	282.02	0.19	106.8	2.64	0.001582932
34339	1361.63	21.99	0.42	883.92	0.73	669.48	1.32	0.001587764
67217	1933.88	21.62	0.87	1205.87	0.93	601.94	2.00	0.001618074
46756	1565.69	26.3	0.66	338.54	0.72	153.63	2.20	0.001622515
32874	1333.42	36.11	0.46	190.41	0.7	204.57	0.93	0.0016362
21747	1157.54	37.44	0.62	556.29	0.69	1338.8	0.42	0.001640266
54421	1679.7	22.6	0.28	332.3	0.52	495.09	0.67	0.001644314
95084	2490.23	24.68	0.62	311.58	0.48	175.73	1.77	0.001659869
50008	1609.75	30.2	0.35	616.41	0.56	760.58	0.81	0.00166788
55001	1689.8	27.55	0.18	229.5	0.41	168.39	1.36	0.001683685
36988	1408.66	39.13	0.47	435.81	0.67	646.42	0.67	0.001694957

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
121413	3080.41	29.98	0.19	267.77	0.41	271.62	0.99	0.00170788
38752	1438.45	36.76	0.95	6299.03	1	8504.24	0.74	0.001752878
62256	1841.75	35.66	0.21	112.4	0.43	119.18	0.94	0.001802147
186609	10999.91	21.37	0.12	3076.39	0.31	3274.45	0.94	0.001816652
49608	1602.74	28.97	0.54	235.82	0.74	309.63	0.76	0.001823402
112515	2864.25	20.15	0.19	481.94	0.38	699.29	0.69	0.001837491
29840	1286.54	29.41	0.15	147.17	0.36	114.15	1.29	0.001847009
85761	2292.02	27.28	0.89	3613.95	0.99	4405.75	0.82	0.001852538
19137	1118.49	37.76	0.13	242.56	0.32	265.68	0.91	0.001864894
22089	1162.54	20.11	0.4	197.65	0.57	300.35	0.66	0.001935978
140570	3677.77	24.5	0.21	667.59	0.4	927.13	0.72	0.001944946
78792	2168.97	32.91	0.81	759.53	0.69	522.68	1.45	0.001948639
32481	1326.57	21.67	0.17	223.38	0.4	165.4	1.35	0.00197206
34017	1354.64	22.14	0.37	285.98	0.19	162.82	1.76	0.002046432
74420	2085.93	22.07	0.26	13007.27	0.45	18146.64	0.72	0.002072882
38879	1439.66	29.82	0.6	1667.3	0.44	238	7.01	0.002098691
42722	1493.63	21.84	0.27	364.08	0.5	305.57	1.19	0.002124981
135412	3510.6	40.24	0.42	282.84	0.65	297.9	0.95	0.002145261
25866	1223.55	27.46	0.27	356.59	0.51	163.06	2.19	0.002146377
136129	3536.46	20.24	0.18	290.21	0.4	201.71	1.44	0.002183214
29538	1281.58	27.09	0.26	297.49	0.49	280.07	1.06	0.002236739
127848	3280.46	22.73	0.19	619.9	0.39	800.21	0.77	0.00231504
149624	4043.64	20.38	0.63	1121.4	0.74	1763.16	0.64	0.002315639
20457	1138.59	19.51	0.19	215.46	0.39	173.69	1.24	0.002339778
146936	3943.83	33.63	0.44	163.49	0.65	196.77	0.83	0.002351086
128936	3311.48	24.33	0.44	251.08	0.24	189.89	1.32	0.002378275
45980	1552.5	37.21	0.9	2996.58	0.97	3580.34	0.84	0.002385109
92841	2430.1	28.33	0.65	329.5	0.84	375.45	0.88	0.002396845
90470	2380.08	36.51	0.21	216.79	0.43	214.85	1.01	0.002409234
24113	1194.55	29.2	0.15	103.2	0.33	161.58	0.64	0.002417535
19871	1130.34	35.39	0.53	558.11	0.64	1079.64	0.52	0.002430554
26879	1238.56	21.14	0.2	332.92	0.43	197.66	1.68	0.002442083
85250	2280.94	36.22	0.14	331.51	0.34	283.49	1.17	0.002444939
53957	1669.69	21.46	0.55	709.99	0.82	528.6	1.34	0.002459676

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
140672	3681.72	32.02	0.2	89.89	0.4	113.44	0.79	0.002463071
6803	928.37	35.46	0.29	45.84	0.44	127.61	0.36	0.002466511
70633	2013.89	31.76	0.32	122.15	0.54	109.6	1.11	0.002480881
76086	2109.92	24.07	0.22	261.69	0.44	219.66	1.19	0.002574392
131932	3399.35	42.1	0.32	339.73	0.53	421.87	0.81	0.002603657
15776	1068.45	24.76	0.96	2690.42	0.97	3231.45	0.83	0.002642976
28103	1257.44	33.92	0.89	4089.39	0.91	5574.78	0.73	0.002662718
126699	3248.53	30.66	0.77	1355.32	0.77	2192.02	0.62	0.00274941
60149	1794.8	23.92	0.77	2895.68	0.96	2213.61	1.31	0.002766739
119292	3035.19	42.02	0.5	792.73	0.68	814.59	0.97	0.002822808
31524	1312.62	20.01	0.21	461.34	0.45	322.5	1.43	0.002832088
18077	1101.47	22.27	0.23	241.67	0.46	198.32	1.22	0.002849063
20750	1141.52	24.51	0.4	216.15	0.55	321.77	0.67	0.002861319
86354	2305.06	34.91	0.14	276.52	0.34	155.45	1.78	0.002923862
83081	2243.97	21.16	0.21	275.97	0.43	213.49	1.29	0.00298167
179035	6650.64	25.54	0.24	389.91	0.47	307.52	1.27	0.003018516
41471	1467.67	21.29	0.37	433.69	0.57	483.82	0.90	0.003041929
149760	4044.92	26.37	0.78	3153.32	0.88	3719.27	0.85	0.003044267
4730	898.32	26.05	0.17	184.1	0.36	335.02	0.55	0.003087261
114823	2926.3	22.22	0.41	620.73	0.64	490.4	1.27	0.003110471
37603	1421.49	37.02	0.16	429.84	0.35	392.2	1.10	0.003118877
70803	2017.88	30.77	0.14	283.92	0.32	265.65	1.07	0.003161555
13747	1025.46	25.6	0.35	282.35	0.54	288.26	0.98	0.003228503
18604	1110.39	33.63	0.45	497.7	0.64	631.07	0.79	0.003257642
113765	2898.31	29.25	0.24	154.8	0.46	140.31	1.10	0.003281968
139455	3630.44	21.78	0.42	641.21	0.69	473.23	1.35	0.003310055
85331	2282.02	22.24	0.65	871.79	0.89	790.4	1.10	0.003332737
130432	3349.42	35.89	0.24	318.83	0.42	340.03	0.94	0.003369281
76839	2128.98	26.97	0.3	109.36	0.48	137.97	0.79	0.003398132
16168	1073.32	35.32	0.95	5164.87	0.94	8234.89	0.63	0.003418263
131548	3384.57	30.83	0.35	137.16	0.17	162.12	0.85	0.003435369
12380	994.43	25.07	0.29	146.65	0.47	166.2	0.88	0.00347091
145238	3858.84	25.85	0.53	1344.15	0.73	1406.8	0.96	0.003490185
28747	1268.57	27.25	0.95	10365.8	0.93	5574.77	1.86	0.003517074

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
141109	3701.74	32.44	0.21	145.46	0.4	219.87	0.66	0.003577469
61192	1816.9	33.75	0.14	182.11	0.3	256.44	0.71	0.003599324
127106	3260.49	41.62	0.22	389.53	0.4	569.3	0.68	0.003620083
3472	875.48	21.94	0.15	107.51	0.33	93.35	1.15	0.003642395
133345	3439.59	39.22	0.51	309.5	0.32	298.12	1.04	0.003807155
67612	1942.84	30.96	0.32	124.69	0.52	138.41	0.90	0.003841914
122623	3114.43	30.29	0.19	153.91	0.35	245.38	0.63	0.003869791
27742	1251.62	22.53	0.21	365.82	0.42	382.48	0.96	0.003882843
18029	1100.5	37.04	0.26	99.54	0.42	269.63	0.37	0.004002599
75248	2096.92	33	0.53	338.55	0.36	231.82	1.46	0.004112489
46542	1561.45	36.96	0.5	393.2	0.68	481.43	0.82	0.004177997
20072	1134.58	23.66	0.54	279.26	0.68	438.98	0.64	0.004205651
47285	1575.75	30.2	0.4	561.74	0.22	439.43	1.28	0.004263712
50056	1610.87	30.29	0.58	2617.31	0.4	2499.12	1.05	0.004303322
63427	1865.81	32.98	0.24	118.04	0.46	107.41	1.10	0.00437236
190524	14109.54	21.93	0.27	1169.35	0.49	956.55	1.22	0.004383509
85627	2289.04	33.59	0.27	188.66	0.46	200.19	0.94	0.004387083
70635	2013.91	25.19	0.97	2173.35	0.96	1584.04	1.37	0.004472113
113439	2889.38	28.65	0.18	142.95	0.36	143.24	1.00	0.00451547
19791	1128.49	25.65	0.29	203.7	0.46	307.04	0.66	0.004595776
84300	2261.03	27.15	0.32	1010.59	0.5	1241.27	0.81	0.004615907
60816	1808.79	23.72	0.4	418.99	0.66	335.75	1.25	0.004768785
110657	2816.33	28.4	0.18	310.01	0.39	146.46	2.12	0.0048116
8390	945.42	25.72	0.34	145.95	0.51	186.18	0.78	0.004839887
79786	2189	26.89	0.64	754.77	0.85	740.66	1.02	0.00484889
74057	2079	24.68	0.47	386.1	0.72	288.99	1.34	0.004851857
35979	1390.44	36.95	0.97	27527.64	0.96	36700.74	0.75	0.005040696
25429	1217.53	35.78	0.26	1889.78	0.43	3416.02	0.55	0.005076705
57888	1746.59	38.21	0.33	322.71	0.54	370.18	0.87	0.005087859
59928	1788.84	29.87	0.28	364.58	0.42	763.85	0.48	0.005212313
56099	1707.81	23.59	0.23	404.84	0.45	221.12	1.83	0.005221556
97463	2544.13	28.26	0.22	170.37	0.41	199.3	0.85	0.005352599
59368	1775.79	31.48	0.44	745.55	0.26	711.64	1.05	0.005370367
29906	1287.59	21.87	0.49	820.27	0.75	774.71	1.06	0.00543093

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
63910	1876.87	22.2	0.9	3082.35	0.99	1652.9	1.86	0.005538579
136790	3559.71	24.92	0.59	1129.69	0.77	1055	1.07	0.005549831
100344	2599.19	28.28	0.73	307.71	0.61	237.91	1.29	0.005599519
127852	3280.56	25.82	0.58	389.96	0.74	526.66	0.74	0.005629617
160089	4436.08	26.32	0.41	1516.37	0.53	3201.34	0.47	0.005665266
86071	2298.99	27.08	0.22	883.62	0.4	1119.47	0.79	0.005677983
59142	1769.71	28.14	0.89	671.18	0.89	483.73	1.39	0.005706788
24449	1199.58	21.95	0.63	558.52	0.76	629.69	0.89	0.00589006
73989	2077.96	22.48	0.17	208.55	0.36	191.03	1.09	0.005918759
91375	2404.01	20.27	0.65	645.16	0.81	795.11	0.81	0.005999377
152744	4160.92	25.82	0.56	4569.88	0.41	2968.4	1.54	0.006055804
127237	3261.5	22.19	0.14	325.42	0.31	298.25	1.09	0.00621858
136789	3559.71	26.52	0.23	398.36	0.43	285.05	1.40	0.00624606
60126	1793.88	32.37	0.5	772.53	0.78	482.76	1.60	0.006336281
24308	1196.52	21	0.4	1020.88	0.6	1015.14	1.01	0.006492346
64899	1892.97	24.56	0.49	538.48	0.64	729.53	0.74	0.006544718
5184	906.18	34.26	0.33	116.94	0.14	233.04	0.50	0.006599227
64067	1878.85	32.18	0.15	139.34	0.32	118.22	1.18	0.006666524
67801	1947.88	31.61	0.45	414.11	0.64	460.56	0.90	0.006709768
88972	2349.04	27.37	0.22	155.27	0.4	191.3	0.81	0.007193872
52446	1645.76	20.61	0.21	318.67	0.4	273.87	1.16	0.007208555
181018	7906.95	19.53	0.18	416.83	0.36	470.1	0.89	0.007361189
13429	1018.46	24.54	0.28	174.53	0.45	194.11	0.90	0.007476475
93417	2446.09	28.37	0.33	141.9	0.49	165.94	0.86	0.007546377
34432	1363.43	36.34	0.98	2453.16	1	2991.62	0.82	0.0076121
110052	2799.08	25.07	0.98	5294.47	1	4023.2	1.32	0.00778777
84704	2269.03	39.33	0.62	247.07	0.51	165.12	1.50	0.007811219
178819	6541.76	20.68	0.22	810.27	0.42	584.36	1.39	0.00783584
137489	3582.7	19.47	0.69	2756.01	0.59	2064.7	1.33	0.007991576
35550	1383.64	38.94	0.15	231.09	0.32	166.52	1.39	0.008017769
37056	1409.58	22.04	0.96	11709.72	1	12667.2	0.92	0.008027411
50384	1616.73	40.25	0.31	859.74	0.15	1010.84	0.85	0.008076916
81181	2210.76	37.06	0.24	196.03	0.44	202.99	0.97	0.008142197
38951	1440.66	39.28	0.4	370.17	0.56	502.54	0.74	0.0084365

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
177971	6236.91	21.07	0.78	2199.25	0.72	1222.24	1.80	0.008442571
69681	1989.88	32.44	0.68	258.98	0.82	308.19	0.84	0.008442671
72483	2045.86	34.17	0.29	675.56	0.49	545.34	1.24	0.00849392
53328	1657.72	22.9	0.19	458.71	0.38	476.97	0.96	0.008548493
62580	1848.81	30.81	0.42	155.4	0.67	122.08	1.27	0.00860141
144344	3817.79	33.54	0.14	91.56	0.3	100.37	0.91	0.008631271
175094	5528.35	28	0.34	428.61	0.19	214.17	2.00	0.008681589
142141	3737.66	37.21	0.21	141.4	0.39	155.09	0.91	0.009073233
71171	2023.91	21.48	0.7	482.48	0.66	377.8	1.28	0.00910369
30524	1296.61	21.69	0.34	657.07	0.19	250.05	2.63	0.00920015
138813	3605.57	21.19	0.22	261.99	0.39	336.18	0.78	0.009346658
63517	1867.95	25.15	0.35	812.49	0.2	194.64	4.17	0.009360851
53393	1658.73	29.94	0.38	479.95	0.51	715.13	0.67	0.009380308
49334	1595.69	20.15	0.31	569.76	0.53	427.14	1.33	0.009488838
118053	3007.41	20.95	0.21	605.01	0.4	466.95	1.30	0.009519109
25099	1212.56	21.2	0.26	186	0.44	184	1.01	0.009553338
36500	1399.62	28.74	0.18	176.03	0.33	204.07	0.86	0.009695384
114086	2907.35	35.96	0.71	289.48	0.59	184.38	1.57	0.009826753
133168	3432.59	32.05	0.88	975.25	0.9	1186	0.82	0.009993548
77684	2148.02	26.04	0.35	1384.49	0.21	392.59	3.53	0.01001899
42216	1483.7	20.65	0.43	696.95	0.65	666.35	1.05	0.01008219
33135	1338.6	23.99	0.83	679.53	0.7	540.09	1.26	0.01010573
143120	3765.6	20.17	0.2	312.06	0.36	394.62	0.79	0.01011999
127443	3266.48	30.07	0.14	107.21	0.31	83.22	1.29	0.01021036
174387	5427.17	22.93	0.21	211.98	0.41	188.96	1.12	0.01024405
18939	1114.48	24.21	0.39	290.71	0.58	265.93	1.09	0.01033476
129131	3318.55	30.99	0.27	128.2	0.43	157.66	0.81	0.01069859
93361	2445.1	28.24	0.21	151.65	0.39	183.1	0.83	0.01089328
174987	5511.28	22.46	0.19	118.66	0.34	149.9	0.79	0.01090952
37124	1410.62	19.9	0.2	165.19	0.36	205.91	0.80	0.01099831
136403	3546.67	26.22	0.19	479.63	0.35	446.44	1.07	0.01119103
129019	3314.43	20.14	0.36	1212.21	0.53	1428.63	0.85	0.01121206
34766	1367.64	38.88	0.72	554.73	0.81	732.36	0.76	0.01136759
77099	2135.96	25.8	0.69	673.94	0.59	429.13	1.57	0.01151054

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
79720	2187.95	39.78	0.94	1515.89	0.97	1750.32	0.87	0.01163086
20756	1141.54	37.33	0.35	181.85	0.48	333.27	0.55	0.01165872
54703	1684.71	29.65	0.19	363.61	0.35	413.98	0.88	0.01205231
32471	1326.56	27.11	0.19	1283.49	0.39	716.64	1.79	0.01209138
91669	2411.08	26.8	0.31	149.25	0.17	100.42	1.49	0.01210806
43442	1507.74	40.02	0.93	1880.51	0.94	2799.68	0.67	0.01213974
76415	2117.93	32.97	0.32	131.04	0.49	143.05	0.92	0.01229273
89604	2360	33.92	0.17	104.7	0.32	117.46	0.89	0.01247033
25363	1216.54	24.24	0.82	1060.15	0.77	1895.59	0.56	0.01248304
132014	3400.58	31.18	0.48	205.96	0.31	213.31	0.97	0.01253784
131589	3385.55	25.49	0.64	2132.01	0.69	3219.82	0.66	0.01264424
74065	2078.93	26.67	0.99	8888.59	1	7324.59	1.21	0.01287456
74273	2081.94	33.66	0.65	647.64	0.73	251.02	2.58	0.01292263
72033	2034.94	25.45	0.35	885.28	0.23	286.88	3.09	0.01305396
114438	2917.36	29.04	0.61	1898.3	0.47	1909.22	0.99	0.01305728
50212	1613.82	23.99	0.57	383.1	0.79	315.83	1.21	0.01345032
130747	3359.58	31.9	0.79	1087.25	0.9	1219.93	0.89	0.01363732
50172	1612.76	23.38	0.2	240.43	0.4	162.08	1.48	0.01368028
127575	3271.49	30.7	0.44	1105.57	0.28	975.34	1.13	0.01386989
13746	1025.47	25	0.14	253.92	0.3	180.17	1.41	0.0139927
146624	3927.82	33.6	0.2	128.49	0.33	207.41	0.62	0.01420281
157882	4352.86	20.17	0.83	5294.82	0.91	6805.13	0.78	0.01436657
54184	1673.76	40.72	0.39	3263.92	0.24	3109.13	1.05	0.01455398
82015	2226.97	33.46	0.65	238.19	0.59	158.17	1.51	0.01466353
81196	2210.95	33.61	0.97	6435.94	1	5197.29	1.24	0.01474302
84909	2274.04	33.51	0.16	177.25	0.31	167.5	1.06	0.01495276
36586	1401.66	40.04	0.23	337.11	0.45	130.86	2.58	0.01499299
46725	1564.72	28.37	0.33	158.99	0.57	109.8	1.45	0.01501347
127731	3276.24	33.38	0.17	99.07	0.31	139.08	0.71	0.01504871
40541	1458.63	27.94	0.22	491.76	0.41	290.64	1.69	0.01506282
67462	1938.88	21.39	0.21	497.65	0.44	125.86	3.95	0.01509124
54438	1679.95	23.82	0.83	13229.37	0.92	22414.37	0.59	0.01516415
51865	1635.76	30.34	0.7	1293.45	0.75	1902.28	0.68	0.01519528
18358	1107.43	25.14	0.33	196.87	0.17	301.02	0.65	0.0154108

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
68117	1954.97	25.36	0.47	564.92	0.32	257.62	2.19	0.01546201
25053	1211.54	25.82	0.26	286.23	0.46	139.23	2.06	0.0162144
53866	1668.81	40.47	0.35	456.9	0.53	446.59	1.02	0.01622193
96879	2529.17	26.99	0.24	141.52	0.43	116.25	1.22	0.01666642
66054	1915	33.63	0.38	183.16	0.24	124.06	1.48	0.01716301
30136	1292.39	36.16	0.26	191.03	0.4	242.41	0.79	0.01741059
120192	3058.38	24.82	0.55	353.37	0.68	410.1	0.86	0.01766189
17899	1098.52	20.89	0.15	205.48	0.31	129.53	1.59	0.01775929
3608	879.5	19.88	0.23	135.29	0.36	148.8	0.91	0.0179793
147000	3945.91	22.03	0.19	565.35	0.31	1053.12	0.54	0.01806868
55484	1695.73	23.18	0.21	299.38	0.39	284.02	1.05	0.01813328
69080	1976.88	32.38	0.52	423.33	0.69	429.91	0.98	0.01813836
38790	1438.66	22.01	0.45	474.69	0.33	257.3	1.84	0.01825064
99691	2582.17	23.67	0.47	288.62	0.35	155.64	1.85	0.01846494
46606	1562.69	22.46	0.56	1915.55	0.72	1837.41	1.04	0.01864284
59149	1769.78	30.98	0.32	364.38	0.19	194.3	1.88	0.01873294
98720	2565.14	23.74	0.44	424.63	0.34	166.37	2.55	0.01935075
69882	1993.88	32.19	0.74	327.73	0.74	159.92	2.05	0.0194273
47402	1576.67	43.3	0.52	3222.02	0.32	4163.23	0.77	0.01946342
143379	3775.75	25.59	0.84	1306.63	0.84	1593.92	0.82	0.0196265
140780	3685.83	22.2	0.59	1264.38	0.67	1945.24	0.65	0.01965948
127354	3264.53	30.66	0.51	273.57	0.69	338.69	0.81	0.01986604
32343	1324.59	28.7	0.23	417.78	0.39	403.57	1.04	0.02013347
48417	1584.51	37.5	0.65	548.77	0.82	499.35	1.10	0.02024919
130803	3361.56	24.24	0.16	202.82	0.31	165.55	1.23	0.02050894
64493	1886.86	27.3	0.28	173.14	0.46	139.99	1.24	0.02091515
64869	1892.77	40.25	0.23	1478.73	0.39	1923.99	0.77	0.02098613
24291	1196.32	36.11	1	27683.09	1	29128.45	0.95	0.02098848
33238	1340.59	28.4	0.3	158.64	0.49	123.38	1.29	0.02106894
4845	900.27	43.66	0.28	894.52	0.42	762.13	1.17	0.02115853
53375	1658.59	21.46	0.18	493.66	0.32	642.58	0.77	0.02122895
54269	1675.71	29.2	0.23	123.18	0.41	93.02	1.32	0.02150144
29279	1276.4	35.92	0.97	4428.57	0.98	5469.42	0.81	0.02156291
26098	1225.32	35.69	0.46	388.09	0.3	484.31	0.80	0.02190198

ID	Polypeptide		Cases		Controls		R	*P* value (Unadjusted)
	Mass (Da)	CE Time (min)	%	MA	%	MA		
50838	1623.73	29.86	0.36	440.08	0.25	131.78	3.34	0.02194621
56011	1705.73	40.44	0.46	363.72	0.31	308.21	1.18	0.02198684
73177	2062.93	26.58	0.87	1114.24	0.92	669.6	1.66	0.02206888
39607	1447.7	19.47	0.57	751.39	0.71	730.22	1.03	0.02257498
63143	1859.83	24.41	0.29	608.61	0.5	298.27	2.04	0.02265832
141019	3697.56	23.7	0.23	279.34	0.38	340.52	0.82	0.02287038
111564	2841.26	24.54	0.68	1865.83	0.73	772.42	2.42	0.02301055
138036	3589.68	25.03	0.66	649.35	0.77	927.04	0.70	0.0230354
28281	1260.56	21.83	0.67	657.29	0.58	494.74	1.33	0.02306255
3796	884.29	43.81	0.29	124.6	0.41	221.26	0.56	0.0232707
130482	3350.55	31.02	0.21	124.17	0.36	129.47	0.96	0.02342008
60975	1812.79	24.14	0.35	287	0.2	544.47	0.53	0.02343743
50766	1622.7	30.44	0.22	461.79	0.39	208.25	2.22	0.02344096
48520	1586.74	28.88	0.44	275.83	0.69	191.67	1.44	0.0235215
97506	2545.12	28.2	0.27	280.79	0.42	276.19	1.02	0.02373503
117009	2977.37	29.12	0.37	166.36	0.47	256.23	0.65	0.0240074
40294	1452.66	23.61	0.68	615.56	0.65	397.31	1.55	0.02404588
19046	1116.53	20.85	0.31	231.33	0.18	277.13	0.83	0.02417943
37662	1422.6	21.72	0.82	4674.93	0.99	3956.25	1.18	0.02458489
58759	1761.83	21.65	0.44	406.97	0.33	294.23	1.38	0.02483642
52320	1643.74	29.53	0.67	382.85	0.88	333.69	1.15	0.02496014
55450	1694.78	23.59	0.15	195.98	0.3	147.07	1.33	0.02515307
42867	1496.63	22.34	0.2	467.24	0.39	235.9	1.98	0.02518309
51328	1632.71	40.15	0.42	665.9	0.27	865.74	0.77	0.02596414
9930	963.49	21.81	0.34	152.37	0.48	182.26	0.84	0.02600125
53800	1667.79	40.56	0.57	419.91	0.39	482.85	0.87	0.02603731
135676	3520.61	30.8	0.36	330.3	0.5	420.67	0.79	0.02603905

%, percentage of samples, in which the polypeptide could be detected; MA, mean signal amplitude of the polypeptides; CE time, capillary electrophoresis migration time. R was calculated as Σ (ln signal amplitude x frequency/number of participants) in controls divided by Σ (ln signal amplitude x frequency/number of participants) in cases. The polypeptides were ordered by ascending *P* value.

Table S3. List of polypeptides included in HF1 with available information on amino-acid sequence

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		
			%	MA		%	MA	R
8725	**GDAGSKGpmV**	**Collagen alpha-1(V)**	**0.05**	**1.94**		**0.63**	**2.28**	**0.067**
123106	RDVEEEEEEEGLEEDAELLTELQEVLG	Coiled-coil and C2 domain-containing protein 1B	0.05	1.98		0.47	2.63	0.080
1577	KGDTGPpGP	Collagen alpha-1(III)	0.05	1.65		0.47	1.85	0.095
103493	DEAGSEADHEGTHSTKRGHAKSRPV	Fibrinogen alpha	0.05	3.36		0.47	3.29	0.109
44146	DDFDAHKALEDDE	Isoform 1 of Histone-lysine N-methyltransferase MLL2	0.11	1.91		0.58	2.49	0.146
4845	GGSGAmGSmD	Immunoglobulin-like and fibronectin type III domain-containing protein 1	0.16	1.55		0.63	2.44	0.161
37610	GPpGpPGSpGEQGPSG	Collagen alpha-1(I)	0.11	1.73		0.53	1.87	0.192
83441	GAVGEKGEPGEAGEpGLpGEGGPpG	Collagen alpha-1(V)	0.11	3.45		0.53	3.56	0.201
74703	KSSSHQDSSRmSSVGDYNT	Bone morphogenetic protein 5	0.11	2.64		0.53	2.7	0.203
101157	GPpGADGQpGAKGEpGDAGAKGDAGpPGPA	Collagen alpha-1(I)	0.11	1.97		0.53	1.98	0.207
103022	FNINNLDNNWLKMHFWFYYA	Dermatan-sulfate epimerase-like protein	0.16	2.52		0.68	2.56	0.232
46091	KGETGDVGQMGppGPP	Collagen alpha-1(V)	0.16	2.08		0.53	2.24	0.280
32022	TYFPHFDLSHG	Hemoglobin subunit alpha	0.21	1.99		0.58	2.21	0.326
82708	GRTGDAGPVGPPGPpGppGpPGPPS	Collagen alpha-1(I)	0.32	2.57		0.84	2.68	0.365
98089	DEAGSEADHEGTHSTKRGHAKSRP	Fibrinogen alpha	0.32	2.97		0.84	3	0.377
61984	**DQDKHDDSTDDSDTDK**	**WW domain-binding protein 11**	**0.53**	**2.64**		**1**	**3.12**	**0.448**
46369	GPpGEKGGQGPPGpQGp	Collagen alpha-1(V)	0.32	2.78		0.68	2.84	0.461
143947	DQGPVGRTGEVGAVGPpGFAGEKGPSGEA GTAGPpGTpGPQG	Collagen alpha-2(I)	0.37	2.26		0.79	2.24	0.472
39275	DGVGQpGLPGpPGPpG	Collagen alpha-1(XVIII)	0.47	2.59		0.79	2.96	0.520
56493	KGDEGEAGDPGDDNNDI	Collagen alpha-1(VI)	0.47	2.56		0.79	2.74	0.556
41972	EQGLpGAAGQDGPpGP	Isoform D preproprotein of collagen alpha-1 (XI)	0.53	2.75		0.84	2.95	0.588
24168	GPpGPPGPSSNQG	Collagen alpha-6(IV)	0.58	2.8		0.84	3.26	0.593
107858	VSESSIHIIGVSLGAHVGGmVGQLFGGQ	Isoform 2 of phospholipase A1 member A	0.63	2.36		0.89	2.69	0.621

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		
			%	MA		%	MA	R
23356	GPpGPpGPSSNQG	Collagen alpha-6(IV)	0.58	2.63		0.84	2.9	0.626
97599	LGSHSQDEEDEDTEYFDAMEDS	101 kDa protein	0.58	2.59		0.89	2.66	0.634
23697	DDGEAGKpGRpG	Collagen alpha-1(I)	0.68	2.8		1	2.88	0.661
36566	EEEDSSDSSSDSE	Isoform 1 of AP-3 complex subunit beta-1	0.58	2.77		0.74	3.27	0.664
26670	GQDGRpGPpGPpG	Collagen alpha-1(I)	0.63	3.02		0.84	3.3	0.686
58050	GPpGEAGKpGEQGVPGDLG	Collagen alpha-1(I)	0.63	2.57		0.84	2.79	0.691
28005	TYFPHFDLSHG	Hemoglobin subunit alpha	0.68	3.08		0.84	3.4	0.733
69979	KGSpGSDGpKGEKGDPGpEGP	Isoform 2C2A' of collagen alpha-2(VI) chain	0.79	2.86		0.95	3.17	0.750
40737	**GPpGPAGNpGpSpNSP**	**Isoform 1 of collagen alpha-1(XXVI)**	**0.84**	**3.33**		**1**	**3.68**	**0.760**
65368	WIDAPDDVFYMATEET	Metastasis-associated protein MTA1 79 kDa protein	0.79	3.17		0.89	3.61	0.779
73434	ADGSDLDAVSHGSmDSGHGTH	C-myc promoter-binding protein isoform 1	0.84	3.1		1	3.28	0.794
108574	DmGPpGPQGPpGKDGPPGVKGENGHPGSP	Isoform 2 of collagen alpha-1 (XIII)	0.79	3.56		0.89	3.85	0.821
90344	GKNGDDGEAGKpGRpGERGPpGPQ	Collagen alpha-1(I)	0.89	3.12		0.95	3.46	0.845
36759	PpGPpGFPGDpGPpG	Collagen alpha-3(V)	0.89	2.94		0.95	3.18	0.866
28561	SpGPDGKTGPpGPA	Collagen alpha-1(I)	0.89	3.36		0.89	3.79	0.886
107460	KNGETGPQGPPGPTGPGGDKGDTGPpGpQG	Collagen alpha-1(III)	0.95	2.91		1	3.11	0.889
32171	ApGDRGEpGPpGPA	Collagen alpha-1(I)	0.95	4.07		1	4.27	0.905
39322	GPpGPpGFPGDPGPpG	Collagen alpha-3(V)	1	3.2		1	3.49	0.917
35339	ApGEDGRpGPpGPQ	Collagen alpha-1(II)	1	3.36		1	3.53	0.952
81196	NGApGNDGAKGDAGApGApGSQGApG	Collagen alpha-1(I)	1	3.72		1	3.59	1.036
41601	DGQPGAKGEpGDAGAK	Collagen alpha-1(I)	1	3.72		1	3.56	1.045
62866	SGpQGppGSEGFTGPPGPQG	Collagen alpha-2(IV)	1	3.89		1	3.71	1.048
99021	QQEQLQQQQFQQQQEQLQQQ	Zinc finger protein 853	1	3.88		1	3.7	1.049
79136	AGPpGEAGKpGEQGVpGDLGApGP	Collagen alpha-1(I)	1	3.74		1	3.49	1.072
50840	DGApGKNGERGGpGGpGP	Collagen alpha-1(III)	0.95	4.17		0.95	3.86	1.080
72533	PpGEAGKpGEQGVpGDLGApGP	Collagen alpha-1(I)	0.95	3.49		0.95	3.21	1.087

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		
			%	MA		%	MA	R
57537	NDGApGKNGERGGpGGpGP	Collagen alpha-1(III)	1	4.02		0.95	3.82	1.108
50212	VGGGEQPPPAPAPRRE	Xylosyltransferase 1	0.89	2.7		0.89	2.43	1.111
60149	GNDGApGKNGERGGpGGpGP	Collagen alpha-1(III)	1	3.72		0.95	3.47	1.128
103198	ERGEAGIpGVpGAKGEDGKDGSpGEpGA	Collagen alpha-1(III)	0.89	2.94		0.89	2.47	1.190
104786	NRGERGSEGSPGHpGQpGppGpPGAPGP	Collagen alpha-1(III)	1	3.58		0.89	3.34	1.204
33135	GAPGPRGRDGEpGT	Isoform 1 of collagen alpha-1(II)	1	2.86		0.89	2.65	1.213
73291	DDKDEEDSPRPRSPPGGPD	Zinc finger and BTB domain-containing protein 46	0.84	2.75		0.79	2.37	1.234
45021	RDGEPGTPGNpGPpGP	Isoform 1 of collagen alpha-1(II)	1	2.82		0.89	2.55	1.243
99475	DDILASPPRLPEPQPYPGAPHHSS	Collagen alpha-1(XVIII)	0.95	2.78		0.89	2.38	1.246
40294	DEPPQSPWDRVK	Apolipoprotein A-I	1	2.85		0.84	2.62	1.295
35424	AMFGPKGFGRGGAE	Cysteine-rich protein 1	0.95	2.79		0.79	2.56	1.311
131294	PGEDGEpGRNGNPGEVGFAGSpGARGFPGAPGLPGL	Collagen alpha-2(V)	1	2.87		0.79	2.71	1.341
111564	ERGEAGIpGVpGAkGEDGKDGSpGEpGANG	Collagen alpha-1(III)	0.89	3.21		0.79	2.67	1.354
104195	NRGERGSEGSPGHPGQPGPpGppGApGP	Collagen alpha-1(III)	0.89	2.61		0.74	2.29	1.371
28747	SpGERGETGPpGP	Collagen alpha-1(III)	1	3.44		0.74	3.32	1.400
44802	GGAGEpGKNGAKGEpGp	Isoform 1 of collagen alpha-1(III)	0.79	2.51		0.63	2.1	1.499
113452	NGEAGSAGPpGppGLRGSpGSRGLPGADGRAG	Collagen alpha-2(I)	0.89	2.47		0.58	2.29	1.655
69681	SNGNpGPpGPSGSpGKDGPpGP	Collagen alpha-1(III)	0.84	2.43		0.42	2.51	1.936
55516	RGSGGGGGGGGQGSTNYGKS	Isoform 3 of heterogeneous nuclear ribonucleoprotein A/B	0.79	2.54		0.42	2.39	1.999
80360	ISVPGPMGPSGPRGLpGPpGApGP	Collagen alpha-1(I)	0.68	2.74		0.26	2.73	2.625
82784	ADGQpGAkGEpGDAGAKGDAGPpGP	Collagen alpha-1(III)	0.63	2.28		0.21	2.31	2.961

ID, polypeptide identifier (SQL number); %, percentage of samples, in which the polypeptide could be detected; MA, mean signal amplitude of the polypeptides. R was calculated as ∑ (ln signal amplitude x frequency/number of participants) in controls divided by ∑ (ln signal amplitude x frequency/number of participants) in cases. The polypeptides were ordered by ascending R.

Table S4. List of polypeptides included in HF2 with available information on amino-acid sequence

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
97599	LGSHSQDEEDEDTEYFDAMEDS	101 kDa protein	0.38	405.88		0.72	558.72	0.73	0.7200787
14071	RVAPEEHPV	Actin, aortic smooth muscle	0.52	984.59		0.71	1197.89	0.82	0.6296769
20750	IHEDPGPPPPS	ACVR2B Activin receptor type-2B	0.4	216.15		0.55	321.77	0.67	0.6146365
72343	EAIPMSIPPEVKFNKPFV	Alpha-1-antitrypsin	0.43	10352.8		0.03	1273.44	8.13	0.7011054
87692	EDPQGDAAQKTDTSHHDQDHP	Alpha-1-antitrypsin	0.15	273.02		0.58	355.4	0.77	0.7264031
107198	FFLPDEGKLQHLENELTHDIITK	Alpha-1-antitrypsin	0.31	15025.57		0.02	2343.04	6.41	0.6427509
67632	EAIPMSIPPEVKFNKPF	Alpha-1-antitrypsin	0.32	13045.5		0.05	4808.08	2.71	0.6349384
90840	MIEQNTKSPLFMGKVVNPTQK	Alpha-1-antitrypsin	0.43	11705.46		0.08	506.56	23.11	0.6810162
136698	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAE	Alpha-1-antitrypsin	0.35	6465.83		0.15	1524.74	4.24	0.6088435
38879	TIDEKGTEAAGAMF	Alpha-1-antitrypsin	0.6	1667.3		0.44	238	7.01	0.6206420
12998	YVVHTNYD	Alpha-1-microglobulin	0.14	130.04		0.44	195.64	0.66	0.6536990
28132	TISEKTSDQIH	Antithrombin-III	0.42	1104.88		0.06	529.33	2.09	0.6821854
40294	DEPPQSPWDRVK	Apolipoprotein A-I	0.68	615.56		0.65	397.31	1.55	0.5920493
29906	LGPHAGDVEGHLS	Apolipoprotein A-IV	0.49	820.27		0.75	774.71	1.06	0.6123512
40487	FHDDGFLAFPGHV	Basement membrane-specific heparan sulfate proteoglycan core protein	0.16	393.55		0.44	238.34	1.65	0.6298895
53393	DAPGQYGAYFHDDGF	Basement membrane-specific heparan sulfate proteoglycan core protein	0.38	479.95		0.51	715.13	0.67	0.5982674
44592	AEPGDPRAMSGRSPP	Beta-1.3-galactosyltransferase 6	0.81	6161.47		0.85	7615.86	0.81	0.6415816
106195	LLKNGERIEKVEHSDLSFSKDWS	Beta-2-microglobulin	0.34	14019.79		0.04	718.01	19.53	0.6506165
45243	VEHSDLSFSKDWS	Beta-2-microglobulin	0.13	725.47		0.4	474.07	1.53	0.6240434
74703	KSSSHQDSSRmSSVGDYNT	Bone morphogenetic protein 5	0.1	318.89		0.42	493.74	0.65	0.6609269
24510	KNDQnTSVSHA	Bromodomain and WD repeat-containing protein 3	0.55	3745.12		0.66	7839.78	0.48	0.6356293

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
74057	SVQPSNHGIYLPSDTQEHA	Isoform 1 of Voltage-dependent R-type calcium channel subunit alpha-1E	0.47	386.1		0.72	288.99	1.34	0.6130952
110657	TTnLEQMMKAGEqGqQqRITFSETG	Cation channel sperm-associated protein 4	0.18	310.01		0.39	146.46	2.12	0.5932185
118597	DGVSGGEGKGGSDGGGSHRKEGEEADAPGVIPG	CD99 antigen	0.78	1741.99		0.95	2083.36	0.84	0.6944090
83081	DGVSGGEGKGGSDGGGSHRKEGEE	CD99 antigen	0.21	275.97		0.43	213.49	1.29	0.6022003
19773	DFDDFNLED	CD99 antigen-like protein 2	0.78	1391.02		0.83	2748.43	0.51	0.6856930
103224	DGVSGGEGKGGSDGGGSHRKEGEEADAPG	CD99 CD99 antigen isoform b precursor	0.15	130.88		0.42	129.08	1.01	0.6310587
68117	SHTSDSDVPSGVTEVVVKL	Clusterin	0.47	564.92		0.32	257.62	2.19	0.5889668
73434	ADGSDLDAVSHGSmDSGHGTH	C-myc promoter-binding protein	0.51	1158.94		0.93	2053.5	0.56	0.8159014
14906	MGPRGPpGPpG	Collagen alpha-1(I) chain	0.37	238.08		0.82	738.97	0.32	0.8186650
78073	AEGSpGRDGSpGAKGDRGETGPA	Collagen alpha-1(I) chain	0.45	904.53		0.88	1576.04	0.57	0.8025085
23697	DDGEAGKpGRpG	Collagen alpha-1(I) chain	0.45	536.63		0.89	884.15	0.61	0.7924107
2659	DDGEAGKpG	Collagen alpha-1(I) chain	0.26	194.46		0.71	568.02	0.34	0.7713648
30575	SpGSpGPDGKTGPp	Collagen alpha-1(I) chain	0.33	1425.18		0.85	1526.54	0.93	0.7771046
28561	SpGPDGKTGPpGPA	Collagen alpha-1(I) chain	0.49	2855.06		0.81	7418.24	0.38	0.7761480
7408	GRpGPpGPpG	Collagen alpha-1(I) chain	0.05	36.97		0.46	169.15	0.22	0.7118410
2505	SpGEAGRpG	Collagen alpha-1(I) chain	0.34	191.41		0.76	383.25	0.50	0.7605761
17694	ApGDRGEpGpP	Collagen alpha-1(I) chain	0.67	3573.1		0.94	5547.8	0.64	0.7645621
43543	GSpGSpGPDGKTGPPGp	Collagen alpha-1(I) chain	0.59	1979.23		0.93	2945.44	0.67	0.7491497
16773	DRGEpGPpGPA	Collagen alpha-1(I) chain	0.09	89		0.46	194.48	0.46	0.6934524
13342	ApGDKGESGPS	Collagen alpha-1(I) chain	0.87	866.5		0.97	1808.79	0.48	0.7371918
57531	TGSpGSpGPDGKTGPPGpAG	Collagen alpha-1(I) chain	0.84	1573.88		0.94	2870.95	0.55	0.7368197
85020	ADGQPGAKGEpGDAGAKGDAGPpGPA	Collagen alpha-1(I) chain	0.46	2506.77		0.81	3634.07	0.69	0.7285289
77763	DGQpGAKGEpGDAGAKGDAGPPGp	Collagen alpha-1(I) chain	0.97	3399.7		0.98	1724.29	1.97	0.7332058
73291	nGDDGEAGKpGRPGERGPpGp	Collagen alpha-1(I) chain	0.86	1417.64		0.73	416.98	3.40	0.7308673

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
15561	GPDGKTGPpGPA	Collagen alpha-1(I) chain	0.04	61.89		0.34	164.52	0.38	0.6542304
99808	LTGPIGPPGpAGApGDKGESGPSGPAGPTG	Collagen alpha-1(I) chain	0.67	449.89		0.9	700.47	0.64	0.7236395
82708	GRTGDAGPVGPPGPpGppGpPGPPS	Collagen alpha-1(I) chain	0.5	396.97		0.78	760.84	0.52	0.7183780
61711	SpGRDGSpGAKGDRGETGP	Collagen alpha-1(I) chain	0.56	877.35		0.28	212.55	4.13	0.6969069
19284	DGRpGPpGPpGA	Collagen alpha-1(I) chain	0.05	270.31		0.35	255.97	1.06	0.6533801
63209	EGSpGRDGSpGAKGDRGET	Collagen alpha-1(I) chain	0.44	1458.34		0.9	1119.04	1.30	0.7149235
14478	SpGPDGKTGPp	Collagen alpha-1(I) chain	0.36	300.27		0.74	286.94	1.05	0.7061543
88282	GANGApGNDGAKGDAGApGApGSQGApG	Collagen alpha-1(I) chain	0.56	594.88		0.84	846.66	0.70	0.7096620
118224	ESGREGApGAEGSpGRDGSpGAKGDRGETGPA	Collagen alpha-1(I) chain	0.64	4554.03		0.91	7727.54	0.59	0.7112564
58084	GPpGPpGKNGDDGEAGKpG	Collagen alpha-1(I) chain	0.58	950.75		0.9	1120.91	0.85	0.7103529
72533	PpGEAGKpGEQGVpGDLGApGP	Collagen alpha-1(I) chain	0.94	3157.59		0.91	1786.23	1.77	0.7108844
90344	GKNGDDGEAGKpGRpGERGPpGPQ	Collagen alpha-1(I) chain	0.68	1380.11		0.93	2542.67	0.54	0.7061543
20862	GLPGPpGPpGPpG	Collagen alpha-1(I) chain	0.31	168.72		0.6	380.82	0.44	0.6882440
73913	GPpGPpGKNGDDGEAGkpGRPG	Collagen alpha-1(I) chain	0.27	649.6		0.6	1056.5	0.61	0.6836735
87365	KNGDDGEAGKpGRpGERGPPGpQ	Collagen alpha-1(I) chain	0.09	185.88		0.39	263.28	0.71	0.6502445
22725	DGAKGDAGApGApG	Collagen alpha-1(I) chain	0.17	65.32		0.46	149.11	0.44	0.6629464
101157	GPpGADGQpGAKGEpGDAGAKGDAGpPGPA	Collagen alpha-1(I) chain	0.09	120.1		0.4	95.3	1.26	0.6487032
55143	PpGEAGKpGEQGVPGDLG	Collagen alpha-1(I) chain	0.43	586.61		0.7	907.46	0.65	0.6860119
38011	PpGKNGDDGEAGKpG	Collagen alpha-1(I) chain	0.09	184.4		0.36	193.02	0.96	0.6406781
122400	ADGQpGAKGEpGDAGAKGDAGpPGPAGPAGPPGpIG	Collagen alpha-1(I) chain	0.64	266.08		0.86	354.59	0.75	0.6901042
77018	DGQPGAKGEpGDAGAKGDAGPPGp	Collagen alpha-1(I) chain	0.96	5570.45		0.95	2768.02	2.01	0.6899447
128435	DRGETGPAGPpGApGAPGAPGPVGpAGKSGDRGETGP	Collagen alpha-1(I) chain	0.24	163.97		0.53	343.3	0.48	0.6662415
58050	GPpGEAGKpGEQGVPGDLG	Collagen alpha-1(I) chain	0.45	409.94		0.74	505.2	0.81	0.6803784
80012	NGDDGEAGkPGRpGERGPpGPQ	Collagen alpha-1(I) chain	0.45	641.13		0.74	794.69	0.81	0.6787840
72896	SGEpGApGSKGDTGAKGEpGPVG	Collagen alpha-1(I) chain	0.92	1350.02		0.96	814.06	1.66	0.6837798
141007	ARGNDGATGAAGPpGPTGPAGppGFpGAVGAKGEAGP QGPRG	Collagen alpha-1(I) chain	0.11	184.21		0.39	260.09	0.71	0.6389775

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
39064	SpGENGApGQMGPRG	Collagen alpha-1(I) chain	0.55	530.59		0.32	213.77	2.48	0.6650723
155132	ARGNDGATGAAGpPGPTGPAGPPGFpGAVGAKGEAGpQGpRGSEGPQG	Collagen alpha-1(I) chain	0.53	337.4		0.69	749.7	0.45	0.6763393
91542	LDGAKGDAGPAGPKGEpGSpGENGApG	Collagen alpha-1(I) chain	0.68	463.41		0.92	572.79	0.81	0.6800595
53744	KpGEQGVpGDLGApGPSG	Collagen alpha-1(I) chain	0.33	264.94		0.63	258.89	1.02	0.6654974
99919	PpGKNGDDGEAGKPGRpGERGppGPQ	Collagen alpha-1(I) chain	0.18	468.84		0.47	666.66	0.70	0.6476403
71602	PpGEAGKpGEQGVpGDLGAPGP	Collagen alpha-1(I) chain	0.91	1846.54		0.91	1008.41	1.83	0.6761798
51175	EGSpGRDGSpGAKGDRG	Collagen alpha-1(I) chain	0.18	210.58		0.46	273.82	0.77	0.6455145
68411	PpGPpGKNGDDGEAGKpGRp	Collagen alpha-1(I) chain	0.23	533.25		0.56	394.1	1.35	0.6532738
42188	GPpGKNGDDGEAGKpG	Collagen alpha-1(I) chain	0.11	642.28		0.36	785.06	0.82	0.6293048
50638	PpGPpGKNGDDGEAGKP	Collagen alpha-1(I) chain	0.31	522.57		0.6	477.87	1.09	0.6563563
75846	GPpGEAGKpGEQGVpGDLGApGP	Collagen alpha-1(I) chain	0.97	2774.85		0.98	1843.41	1.51	0.6703869
56139	pPGEAGKpGEQGVpGDLG	Collagen alpha-1(I) chain	0.71	818.24		0.89	1465.01	0.56	0.6694303
61576	GANGApGNDGAKGDAGApGApG	Collagen alpha-1(I) chain	0.32	298.73		0.61	357.37	0.84	0.6549213
102819	GPpGKNGDDGEAGKPGRpGERGPpGpQ	Collagen alpha-1(I) chain	0.3	448.42		0.54	706.56	0.63	0.6485969
108724	KEGGKGPRGETGPAGRpGEVGpPGPpGPAG	Collagen alpha-1(I) chain	0.29	183.13		0.51	322.27	0.57	0.6461522
105105	KDGEAGAQGPpGPAGPAGERGEQGPAGSpG	Collagen alpha-1(I) chain	0.13	64.83		0.36	112.37	0.58	0.6250531
23628	KpGEQGVpGDLG	Collagen alpha-1(I) chain	0.18	151.25		0.45	146.39	1.03	0.6355230
32171	ApGDRGEpGPpGPA	Collagen alpha-1(I) chain	0.97	8865.26		0.96	18773.43	0.47	0.6632653
130077	GPpGESGREGApGAEGSpGRDGSpGAKGDRGETGPA	Collagen alpha-1(I) chain	0.21	466		0.45	762.99	0.61	0.6363202
81457	IGPpGPAGApGDKGESGPSGPAGPTG	Collagen alpha-1(I) chain	0.55	216.02		0.73	376.59	0.57	0.6583759
62547	DAGPVGPpGPpGPpGPPGPPS	Collagen alpha-1(I) chain	0.15	144.9		0.38	350.11	0.41	0.6245748
98485	PQGFqGPpGEPGEPGASGPMGpRGPpG	Collagen alpha-1(I) chain	0.23	138.35		0.52	111.61	1.24	0.6389243
82026	GNSGEpGApGSKGDTGAKGEpGPVG	Collagen alpha-1(I) chain	0.6	13874.99		0.85	17489.37	0.79	0.6572066
58941	GPpGEAGKpGEQGVpGDLG	Collagen alpha-1(I) chain	0.7	1567.7		0.84	2259.23	0.69	0.6574724
28850	DGQPGAKGEpGDAG	Collagen alpha-1(I) chain	0.15	159.62		0.39	185.38	0.86	0.6213329
68663	GEpGApGSKGDTGAKGEpGPVG	Collagen alpha-1(I) chain	0.47	519.19		0.21	557.78	0.93	0.6301020

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
106067	PpGADGQpGAKGEpGDAGAKGDAGPpGPAGP	Collagen alpha-1(I) chain	0.22	134.31		0.48	149.06	0.90	0.6304209
124886	PpGESGREGAPGAEGSpGRDGSpGAKGDRGETGP	Collagen alpha-1(I) chain	0.46	1372.7		0.74	1238.23	1.11	0.6467368
108021	GPpGADGQPGAKGEpGDAGAKGDAGpPGPAGP	Collagen alpha-1(I) chain	0.67	306.74		0.79	450.84	0.68	0.6494473
26670	GQDGRpGPpGPpG	Collagen alpha-1(I) chain	0.5	849.6		0.57	2832.67	0.30	0.6425914
65312	ETGPAGRpGEVGPpGPpGPAG	Collagen alpha-1(I) chain	0.18	204.42		0.43	186.61	1.10	0.6217049
118163	LTGSpGSpGpDGKTGPPGPAGQDGRPGPpGppG	Collagen alpha-1(I) chain	0.89	1143.92		0.94	1539.79	0.74	0.6492347
42594	VGPpGpPGPPGPPGPPS	Collagen alpha-1(I) chain	0.55	381.96		0.71	561.66	0.68	0.6430697
55582	NGApGNDGAKGDAGApGApG	Collagen alpha-1(I) chain	0.87	1006.3		0.94	1338.55	0.75	0.6439201
86677	ADGQpGAKGEpGDAGAKGDAGppGPA	Collagen alpha-1(I) chain	0.33	200.55		0.56	221.45	0.91	0.6296769
107858	RPGApGPAGARGnDGATGAAGPPGPTGpAGpP	Collagen alpha-1(I) chain	0.48	313.21		0.67	439.04	0.71	0.6360544
102371	KEGGKGPRGETGPAGRpGEVGpPGPpGP	Collagen alpha-1(I) chain	0.33	297.28		0.54	384.8	0.77	0.6277636
65257	SGEpGApGSKGDTGAKGEpGP	Collagen alpha-1(I) chain	0.43	230.8		0.26	91.2	2.53	0.6195791
89642	GKNGDDGEAGKPGRpGERGPpGPQ	Collagen alpha-1(I) chain	0.3	279.82		0.48	531.27	0.53	0.6224490
16779	ApGDRGEpGPP	Collagen alpha-1(I) chain	0.17	206.52		0.39	191.34	1.08	0.6097470
85076	ADGqPGAKGEpGDAGAKGDAGPpGPA	Collagen alpha-1(I) chain	0.6	2154.86		0.44	1128.52	1.91	0.6307398
27350	DKGETGEQGDRG	Collagen alpha-1(I) chain	0.79	1332.67		0.98	1454.94	0.92	0.6381803
92410	LDGAKGDAGpAGPKGEpGSpGENGApG	Collagen alpha-1(I) chain	0.62	250.12		0.83	286.44	0.87	0.6344600
152967	ERGEQGPAGSpGFQGLpGpAGppGEAGKpGEQGVPGD LGAPGPSG	Collagen alpha-1(I) chain	0.82	824.03		0.85	1355.53	0.61	0.6328656
42776	EpGDAGAKGDAGPpGPA	Collagen alpha-1(I) chain	0.49	285.32		0.72	284.56	1.00	0.6289328
55315	PpGPPGkNGDDGEAGKpG	Collagen alpha-1(I) chain	0.13	174.77		0.34	139.73	1.25	0.5985863
67217	GDDGEAGKPGRpGERGPpGP	Collagen alpha-1(I) chain	0.87	1205.87		0.93	601.94	2.00	0.6310055
21747	GPPGPpGppGPPS	Collagen alpha-1(I) chain	0.62	556.29		0.69	1338.8	0.42	0.6281888
50008	TGSpGSpGPDGKTGPpGP	Collagen alpha-1(I) chain	0.35	616.41		0.56	760.58	0.81	0.6195791
29840	DGQpGAKGEpGDAG	Collagen alpha-1(I) chain	0.15	147.17		0.36	114.15	1.29	0.5995429
85761	ADGQpGAKGEpGDAGAKGDAGPpGPA	Collagen alpha-1(I) chain	0.89	3613.95		0.99	4405.75	0.82	0.6294111
74420	EGSpGRDGSpGAKGDRGETGPA	Collagen alpha-1(I) chain	0.26	13007.27		0.45	18146.64	0.72	0.6091093

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
29538	SpGSPGPDGKTGPp	Collagen alpha-1(I) chain	0.26	297.49		0.49	280.07	1.06	0.6101722
127848	pPGESGREGApGAEGSpGRDGSpGAKGDRGETGPA	Collagen alpha-1(I) chain	0.19	619.9		0.39	800.21	0.77	0.6013499
128936	SPGEAGRPGEAGLpGAKGLTGSPGSPGpDGkTGPPGP	Collagen alpha-1(I) chain	0.44	251.08		0.24	189.89	1.32	0.6066645
92841	ADGQPGAKGEpGDAGAKGDAGPpGPAGP	Collagen alpha-1(I) chain	0.65	329.5		0.84	375.45	0.88	0.6252126
114823	ESGREGAPGAEGSpGRDGSpGAKGDRGETGP	Collagen alpha-1(I) chain	0.41	620.73		0.64	490.4	1.27	0.6159651
70803	GEpGEpGASGPMGPRGPpGPpG	Collagen alpha-1(I) chain	0.14	283.92		0.32	265.65	1.07	0.5907738
13747	PpGSAGAPGKDG	Collagen alpha-1(I) chain	0.35	282.35		0.54	288.26	0.98	0.6113946
76839	DGKTGpPGPAGQDGRPGPpGppG	Collagen alpha-1(I) chain	0.3	109.36		0.48	137.97	0.79	0.6068240
12380	GPDGKTGPpGP	Collagen alpha-1(I) chain	0.29	146.65		0.47	166.2	0.88	0.6057611
75248	GApGNDGAKGDAGApGApGSQGApG	Collagen alpha-1(I) chain	0.53	338.55		0.36	231.82	1.46	0.6088435
63427	DAGPAGPKGEpGSpGENGApG	Collagen alpha-1(I) chain	0.24	118.04		0.46	107.41	1.10	0.6009779
70635	NSGEpGApGSKGDTGAKGEpGP	Collagen alpha-1(I) chain	0.97	2173.35		0.96	1584.04	1.37	0.6181973
79786	ADGQPGAKGEPGDAGAKGDAGPpGP	Collagen alpha-1(I) chain	0.64	754.77		0.85	740.66	1.02	0.6161777
63910	DDGEAGKPGRPGERGpPGp	Collagen alpha-1(I) chain	0.9	3082.35		0.99	1652.9	1.86	0.6153274
100344	AGPpGApGApGApGPVGPAGKSGDRGETGP	Collagen alpha-1(I) chain	0.73	307.71		0.61	237.91	1.29	0.6132015
127852	AAGEPGKAGERGVpGppGAVGPAGKDGEAGAQGPpGP	Collagen alpha-1(I) chain	0.58	389.96		0.74	526.66	0.74	0.6128295
73989	GDDGEAGKpGRpGERGPpGPQ	Collagen alpha-1(I) chain	0.17	208.55		0.36	191.03	1.09	0.5892326
88972	GADGQPGAkGEpGDAGAKGDAGPpGPA	Collagen alpha-1(I) chain	0.22	155.27		0.4	191.3	0.81	0.5915179
93417	ADGQpGAKGEpGDAGAKGDAGpPGPAGP	Collagen alpha-1(I) chain	0.33	141.9		0.49	165.94	0.86	0.5988520
54703	EpGSpGENGAPGQmGPR	Collagen alpha-1(I) chain	0.19	363.61		0.35	413.98	0.88	0.5819515
43442	VGPpGPpGPpGPPGPPS	Collagen alpha-1(I) chain	0.93	1880.51		0.94	2799.68	0.67	0.6042730
132014	GPpGADGQPGAKGEpGDAGAKGDAGpPGPAGPAGPPGPIG	Collagen alpha-1(I) chain	0.48	205.96		0.31	213.31	0.97	0.5917304
130747	PpGADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPpGPIG	Collagen alpha-1(I) chain	0.79	1087.25		0.9	1219.93	0.89	0.6023597
50172	ApGSKGDTGAKGEpGPVG	Collagen alpha-1(I) chain	0.2	240.43		0.4	162.08	1.48	0.5830145
82015	NGApGNDGAkGDAGApGApGSQGApG	Collagen alpha-1(I) chain	0.65	238.19		0.59	158.17	1.51	0.5987457

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
81196	NGApGNDGAKGDAGApGApGSQGApG	Collagen alpha-1(I) chain	0.97	6435.94		1	5197.29	1.24	0.6014031
84909	GLpGpAGpPGEAGKPGEQGVpGDLG	Collagen alpha-1(I) chain	0.16	177.25		0.31	167.5	1.06	0.5754677
40541	SpGENGApGQmGPRG	Collagen alpha-1(I) chain	0.22	491.76		0.41	290.64	1.69	0.5832270
25053	GPpGEAGKpGEQG	Collagen alpha-1(I) chain	0.26	286.23		0.46	139.23	2.06	0.5855655
96879	GETGPAGRpGEVGPpGPpGPAGEKGSpG	Collagen alpha-1(I) chain	0.24	141.52		0.43	116.25	1.22	0.5836522
63143	NSGEpGApGSKGDTGAKGEp	Collagen alpha-1(I) chain	0.29	608.61		0.5	298.27	2.04	0.5834396
60975	GEpGApGSKGDTGAKGEpGP	Collagen alpha-1(I) chain	0.35	287		0.2	544.47	0.53	0.5739796
97506	GPpGADGQpGAKGEpGDAGAKGDAGpPGP	Collagen alpha-1(I) chain	0.27	280.79		0.42	276.19	1.02	0.5794005
58759	DGEAGKpGRPGERGPpGP	Collagen alpha-1(I) chain	0.44	406.97		0.33	294.23	1.38	0.5818452
5675	DGKTGPpGPA	Collagen alpha-1(I) chain	0.29	266.81		0.85	709.73	0.38	0.8384354
121775	ADGQPGAkGEPGDAGAKGDAGPPGPAGpAGpPGPIG	Collagen alpha-1(I) chain	0.64	333.92		0.76	477.73	0.70	0.6411033
36988	GPPGppGPpGPPGPPS	Collagen alpha-1(I) chain	0.47	435.81		0.67	646.42	0.67	0.6251063
33135	GAPGPRGRDGEpGT	Collagen alpha-1(II)	0.83	679.53		0.7	540.09	1.26	0.6062394
35339	ApGEDGRpGPpGPQ	Collagen alpha-1(II) chain	0.95	2232.32		1	3398.04	0.66	0.7731718
16976	DGpSGAEGpPGp	Collagen alpha-1(II) chain	0.92	1900.2		0.95	2435.82	0.78	0.6693240
93227	GpAGPPGEKGEPGDDGPSGAEGPpGPQ	Collagen alpha-1(II) chain	0.79	708.3		0.94	855.09	0.83	0.6675170
23968	pPGSNGNpGPpGP	Collagen alpha-1(II) chain	0.23	206.01		0.46	401.04	0.51	0.6308461
61192	VGPSGApGEDGRpGPpGPQG	Collagen alpha-1(II) chain	0.14	182.11		0.3	256.44	0.71	0.5880102
32470	SpGGpGSDGKpGPpG	Collagen alpha-1(III) chain	0.35	218.46		0.72	362.3	0.60	0.7372449
30699	DGApGKNGERGGpG	Collagen alpha-1(III) chain	0.39	428.35		0.84	409.15	1.05	0.7392645
18943	SpGERGETGPp	Collagen alpha-1(III) chain	0.82	2185.57		0.93	4029.69	0.54	0.7357568
123969	GERGSpGGpGAAGFpGARGLpGpPGSNGNPGPpGp	Collagen alpha-1(III) chain	0.86	1809.86		0.74	981.31	1.84	0.7189626
107460	KNGETGPQGPPGPTGPGGDKGDTGPpGpQG	Collagen alpha-1(III) chain	0.86	919.94		0.96	1398.45	0.66	0.7167304
1577	KGDTGPpGP	Collagen alpha-1(III) chain	0.15	107.18		0.5	205.69	0.52	0.6786777
18988	DGESGRpGRpG	Collagen alpha-1(III) chain	0.07	422.96		0.39	340.14	1.24	0.6550276
156081	ARGNDGARGSDGQpGppGPPGTAGFPGSpGAKGEVGpAGSpGSNGApG	Collagen alpha-1(III) chain	0.46	2355		0.74	3896.07	0.60	0.6979698

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
104786	NRGERGSEGSPGHpGQpGppGpPGAPGP	Collagen alpha-1(III) chain	0.97	3608.38		0.91	2259.68	1.60	0.7008397
110913	LRGGAGpPGPEGGKGAAGpPGppGAAGTPGLQG	Collagen alpha-1(III) chain	0.5	386.13		0.75	629.26	0.61	0.6930272
105352	NRGERGSEGSpGHpGQpGppGPPGAPGp	Collagen alpha-1(III) chain	0.97	5094.04		0.96	3271.88	1.56	0.6905825
98596	ApGPAGSRGApGPQGpRGDKGETGERG	Collagen alpha-1(III) chain	0.64	1170.12		0.89	1512.92	0.77	0.6864902
63135	NpGPPGpSGSpGKDGPpGPAG	Collagen alpha-1(III) chain	0.18	299.62		0.47	403	0.74	0.6490221
38798	GLpGTGGPpGENGKpG	Collagen alpha-1(III) chain	0.88	3752.67		1	4550.73	0.82	0.6778274
156445	ARGNDGARGSDGQpGpPGPpGTAGFpGSpGAKGEVGpAGSpGSNGApG	Collagen alpha-1(III) chain	0.86	1787.33		0.96	2673.53	0.67	0.6731505
106678	KNGETGPQGPPGPTGPGGDKGDTGPpGPQG	Collagen alpha-1(III) chain	0.23	195.1		0.48	200.14	0.97	0.6410502
3743	PpGENGKpG	Collagen alpha-1(III) chain	0.21	97.1		0.47	132.98	0.73	0.6367453
61304	GLpGTGGPpGENGKPGEPGp	Collagen alpha-1(III) chain	0.63	3412.56		0.53	646.82	5.28	0.6544430
62000	ApGApGGKGDAGApGERGPpG	Collagen alpha-1(III) chain	0.55	464.05		0.33	226.66	2.05	0.6451956
48394	NDGApGKNGERGGpGGp	Collagen alpha-1(III) chain	0.51	561.63		0.79	543.66	1.03	0.6557185
71312	SEGSpGHpGQpGpPGPPGApGp	Collagen alpha-1(III) chain	0.94	1078.97		0.92	674.42	1.60	0.6576318
88093	ERGSEGSPGHpGQPGpPGPpGApGP	Collagen alpha-1(III) chain	0.43	261.05		0.21	89.41	2.92	0.6282951
156878	LQGLpGTGGppGENGKpGEpGpKGDAGAPGAPGGKGDAGAPGERGppG	Collagen alpha-1(III) chain	0.33	3184.53		0.11	966.74	3.29	0.6122449
61340	GLpGTGGPpGEnGKPGEpGP	Collagen alpha-1(III) chain	0.32	839.62		0.13	71.66	11.72	0.6100128
49295	ApGGKGDAGApGERGPpG	Collagen alpha-1(III) chain	0.81	711.82		0.81	330.8	2.15	0.6493410
97349	KNGETGPQGPPGPTGPGGDKGDTGPpGP	Collagen alpha-1(III) chain	0.13	208.47		0.36	112.03	1.86	0.6128295
50840	DGApGKNGERGGpGGpGP	Collagen alpha-1(III) chain	0.89	9939.06		0.99	5733.56	1.73	0.6448236
61945	GLpGTGGPpGENGKpGEPGp	Collagen alpha-1(III) chain	0.78	6969.39		0.77	1660.16	4.20	0.6419005
19655	GGpGSDGKpGPpG	Collagen alpha-1(III) chain	0.41	152.24		0.16	224.59	0.68	0.6124575
61332	ApGAPGGKGDAGApGERGPpG	Collagen alpha-1(III) chain	0.95	5644.1		0.99	6228.52	0.91	0.6409970
96716	LRGGAGPpGPEGGKGAAGPpGPpGAAGTpG	Collagen alpha-1(III) chain	0.49	548.94		0.63	841.82	0.65	0.6342474
57537	NDGApGKNGERGGpGGpGP	Collagen alpha-1(III) chain	0.91	5998.4		0.99	5980.02	1.00	0.6380208
97965	KNGETGPQGPpGPTGPGGDKGDTGPPGp	Collagen alpha-1(III) chain	0.29	185.08		0.51	152.9	1.21	0.6185162

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
15887	GpGSDGKpGPpG	Collagen alpha-1(III) chain	0.44	139.18		0.57	232.32	0.60	0.6254783
78792	SDGQpGPpGPpGTAGFpGSpGAKG	Collagen alpha-1(III) chain	0.81	759.53		0.69	522.68	1.45	0.6277636
25866	GPGGDKGDTGPpGP	Collagen alpha-1(III) chain	0.27	356.59		0.51	163.06	2.19	0.6119260
70633	AGpPGPPGppGTSGHpGSpGSpG	Collagen alpha-1(III) chain	0.32	122.15		0.54	109.6	1.11	0.6134141
60149	GNDGApGKNGERGGpGGpGP	Collagen alpha-1(III) chain	0.77	2895.68		0.96	2213.61	1.31	0.6242560
85331	ApGHpGPpGPVGPAGKSGDRGESGP	Collagen alpha-1(III) chain	0.65	871.79		0.89	790.4	1.10	0.6212798
28747	SpGERGETGPpGP	Collagen alpha-1(III) chain	0.95	10365.8		0.93	5574.77	1.86	0.6213329
27742	DGVPGKDGPRGPT	Collagen alpha-1(III) chain	0.21	365.82		0.42	382.48	0.96	0.5988520
84300	LQGLpGTGGPpGENGKpGEpGPKG	Collagen alpha-1(III) chain	0.32	1010.59		0.5	1241.27	0.81	0.6048044
13429	SpGGKGEmGPA	Collagen alpha-1(III) chain	0.28	174.53		0.45	194.11	0.90	0.5956101
69681	SNGNpGPpGPSGSpGKDGPpGP	Collagen alpha-1(III) chain	0.68	258.98		0.82	308.19	0.84	0.6086841
71171	GEPGGkGERGApGEKGEGGpPG	Collagen alpha-1(III) chain	0.7	482.48		0.66	377.8	1.28	0.6066645
77099	GDAGApGApGGKGDAGApGERGPpG	Collagen alpha-1(III) chain	0.69	673.94		0.59	429.13	1.57	0.6026786
32471	SpGGpGSDGKpGpPG	Collagen alpha-1(III) chain	0.19	1283.49		0.39	716.64	1.79	0.5834928
76415	SNGNpGpPGPSGSPGKDGPpGpAG	Collagen alpha-1(III) chain	0.32	131.04		0.49	143.05	0.92	0.5923151
74065	DAGApGApGGKGDAGApGERGPpG	Collagen alpha-1(III) chain	0.99	8888.59		1	7324.59	1.21	0.6034226
127575	NTGApGSpGVSGpKGDAGQpGEKGSPGAQGPPGAPGp	Collagen alpha-1(III) chain	0.44	1105.57		0.28	975.34	1.13	0.5879571
67462	kGNDGApGKNGERGGpGGpGP	Collagen alpha-1(III) chain	0.21	497.65		0.44	125.86	3.95	0.5840774
120192	QNGEPGGKGERGApGEKGEGGppGVAGPpGGSGP	Collagen alpha-1(III) chain	0.55	353.37		0.68	410.1	0.86	0.5957696
69882	SEGSPGHpGQPGpPGpPGApGP	Collagen alpha-1(III) chain	0.74	327.73		0.74	159.92	2.05	0.5963542
32343	TGPGGDKGDTGPpGP	Collagen alpha-1(III) chain	0.23	417.78		0.39	403.57	1.04	0.5791348
54269	GpPGPpGTSGHpGSpGSpG	Collagen alpha-1(III) chain	0.23	123.18		0.41	93.02	1.32	0.5791348
73177	DAGApGAPGGKGDAGApGERGPpG	Collagen alpha-1(III) chain	0.87	1114.24		0.92	669.6	1.66	0.5951318
111564	ERGEAGIpGVpGAkGEDGKDGSpGEpGANG	Collagen alpha-1(III) chain	0.68	1865.83		0.73	772.42	2.42	0.5933248
33209	SpGERGETGPpGPA	Collagen alpha-1(III) chain	0.45	180.64		0.65	214.9	0.84	0.6281888
53800	GPPGFTGPpGPpGPPGPPG	Collagen alpha-1(IV) chain	0.57	419.91		0.39	482.85	0.87	0.5857781

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
46091	KGETGDVGQMGppGPP	Collagen alpha-1(V)	0.18	150.82		0.51	126.48	1.19	0.6576318
56493	KGDEGEAGDPGDDNNDI	Collagen alpha-1(VI)	0.24	416.31		0.7	672.93	0.62	0.7493622
54421	ppGDSGppGEKGDPGRP	Collagen alpha-1(VII) chain	0.28	332.3		0.52	495.09	0.67	0.6156463
20756	GPpGPpGPPGPpA	Collagen alpha-1(VIII) chain	0.35	181.85		0.48	333.27	0.55	0.5936437
33973	KGEAGLpGApGSPGQ	Collagen alpha-1(XIX) chain	0.68	312.44		0.89	463.05	0.67	0.6986076
37903	GLPGPpGPpGSFLSN	Collagen alpha-1(XVII) chain	0.86	1563.29		0.98	2260.54	0.69	0.6799532
22835	GPpGPpGPpGPVT	Collagen alpha-1(XVII) chain	0.26	186.97		0.46	281.09	0.67	0.6215986
91342	DDILASPPRLPEPQPYPGAPHH	Collagen alpha-1(XVIII) chain	0.45	333.4		0.15	222.75	1.50	0.6684736
99475	DDILASPPRLPEPQPYPGAPHHSS	Collagen alpha-1(XVIII) chain	0.87	691.24		0.9	332.35	2.08	0.7035502
34766	PpGPpGPpGPPGTPV	Collagen alpha-1(XVIII) chain	0.72	554.73		0.81	732.36	0.76	0.6045918
50838	DpGKDGVGQpGLpGppG	Collagen alpha-1(XVIII) chain	0.36	440.08		0.25	131.78	3.34	0.5775935
48520	QGpRGQpGPPGpPGApG	Collagen alpha-1(XXIV) chain	0.44	275.83		0.69	191.67	1.44	0.5901361
6803	GPpGPYGnPG	Collagen alpha-1(XXVII) chain	0.29	45.84		0.44	127.61	0.36	0.6082058
41434	GpSGPpGPDGNKGEpG	Collagen alpha-2(I) chain	0.35	426.47		0.72	472.77	0.90	0.7190689
80306	NDGPpGRDGQpGHKGERGYpG	Collagen alpha-2(I) chain	0.17	374.8		0.5	495.49	0.76	0.6717687
36769	DGPpGRDGQpGHKG	Collagen alpha-2(I) chain	0.19	290.39		0.52	365.14	0.80	0.6745323
114702	TGEVGAVGpPGFAGEKGpSGEAGTAGPpGTpGP	Collagen alpha-2(I) chain	0.26	171.24		0.57	254.69	0.67	0.6767113
120423	EAGRDGNpGNDGPpGRDGQpGHkGERGYPG	Collagen alpha-2(I) chain	0.28	453.18		0.56	815	0.56	0.6762330
151244	SKGESGNKGEpGSAGPQGPpGPSGEEGKRGPNGEAGSAGPpGPpG	Collagen alpha-2(I) chain	0.62	747.28		0.81	1311.78	0.57	0.6813350
24958	GPpGPDGNKGEpG	Collagen alpha-2(I) chain	0.43	509.5		0.69	602.63	0.85	0.6617772
60248	QGEAGQKGDAGAPGpQGpSG	Collagen alpha-2(I) chain	0.24	243.77		0.52	219.24	1.11	0.6454082
143947	DQGPVGRTGEVGAVGPpGFAGEKGPSGEAGTAGPpGTpGPQG	Collagen alpha-2(I) chain	0.43	201.71		0.66	318.74	0.63	0.6538053
102725	QGPpGPSGEEGKRGPNGEAGSAGPpGPpG	Collagen alpha-2(I) chain	0.73	374.49		0.88	483.16	0.78	0.6551871
139064	DQGPVGRTGEVGAVGPpGFAGEKGPSGEAGTAGpPGTpGP	Collagen alpha-2(I) chain	0.57	285.22		0.7	423.62	0.67	0.6406250

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
4976	DpGKNGDKG	Collagen alpha-2(I) chain	0.76	514.64		0.9	730.44	0.70	0.6426446
112515	GRDGNpGNDGPpGRDGQpGHKGERGYpG	Collagen alpha-2(I) chain	0.19	481.94		0.38	699.29	0.69	0.6029974
126699	RTGEVGAVGpPGFAGEKGPSGEAGTAGPPGTpGpQG	Collagen alpha-2(I) chain	0.77	1355.32		0.77	2192.02	0.62	0.6237245
19791	ApGEAGRDGNpG	Collagen alpha-2(I) chain	0.29	203.7		0.46	307.04	0.66	0.6021471
144344	DQGPVGRTGEVGAVGPpGFAGEKGpSGEAGTAGPpGTpGPQG	Collagen alpha-2(I) chain	0.14	91.56		0.3	100.37	0.91	0.5794005
114086	TGEVGAVGPpGFAGEKGPSGEAGTAGPpGTpGP	Collagen alpha-2(I) chain	0.71	289.48		0.59	184.38	1.57	0.6051233
127354	RTGEVGAVGpPGFAGEkGPSGEAGTAGPPGTpGpQG	Collagen alpha-2(I) chain	0.51	273.57		0.69	338.69	0.81	0.5936437
117009	VGEpGPAGSKGESGNKGEPGSAGPqGPpGpSGE	Collagen alpha-2(I) chain	0.37	166.36		0.47	256.23	0.65	0.5840774
55450	GpAGpAGPRGSpGERGEV	Collagen alpha-2(I) chain	0.15	195.98		0.3	147.07	1.33	0.5682929
3052	ApGERGPpG	Collagen alpha-2(IV) chain	0.4	84.26		0.57	230.43	0.37	0.6354698
84484	pGFPGAQGEPGSQGEpGDpGLpGP	Collagen alpha-2(IV) chain	0.35	226.09		0.15	173.73	1.30	0.6014031
20072	PIGQEGAPGRPG	Collagen alpha-2(IV) chain	0.54	279.26		0.68	438.98	0.64	0.6153805
98891	PGSAGPPGSPGPQGSTGPQGIRGqPGDPG	Collagen alpha-2(V) chain	0.71	265.4		0.54	135.09	1.96	0.6669855
121940	LTGNpGVQGPEGKLGPLGApGEDGRpGpPGSIG	Collagen alpha-2(V) chain	0.71	485.63		0.89	725.01	0.67	0.6641156
69979	KGSpGSDGpKGEKGDPGpEGP	collagen alpha-2(VI) chain	0.39	720.87		0.86	1396.18	0.52	0.7988946
43828	SpGSDGPKGEKGDpGP	Collagen alpha-2(VI) chain	0.45	198.48		0.26	115.21	1.72	0.6176658
61405	GpPGEGRAGEpGTAGpTGpP	Collagen alpha-2(VIII) chain	0.34	460.77		0.63	562.02	0.82	0.6535927
61404	GPpGEGRAGEpGTAGpTGpP	Collagen alpha-2(VIII) chain	0.11	762.89		0.31	243.75	3.13	0.5954507
64067	pGFPGTpGLpGmPGHDGAPG	Collagen alpha-5(IV) chain	0.15	139.34		0.32	118.22	1.18	0.5841305
74273	GQDGIPGPAGqKGEPGqpGFGN	Collagen alpha-5(IV) chain	0.65	647.64		0.73	251.02	2.58	0.6018282
18029	pGPPGpPGpPSP	Collagen alpha-6(IV) chain	0.26	99.54		0.42	269.63	0.37	0.6005527
72641	pGppGppGSAGARGEpGpGGRp	Collagen. type XII. alpha 1	0.98	4334.17		0.96	1332.88	3.25	0.7834821
66197	DELPAKDDPDAPLQPVTP	Complement C4-A	0.35	161.44		0.6	147.17	1.10	0.6308461
42866	MIPGGLSEAKPATPE	Cystatin-A	0.23	299.77		0.57	229.35	1.31	0.6600234
103022	FNINNLDNNWLKMHFWFYYA	Dermatan-sulfate epimerase-like protein	0.14	617.79		0.39	354.22	1.74	0.6128827

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
38910	DEAGSEADHEGTHS	Fibrinogen alpha chain	0.3	613.88		0.63	406.33	1.51	0.6530612
61573	DEAGSEADHEGTHSTKR	Fibrinogen alpha chain	0.73	2839.49		0.94	3352.31	0.85	0.6515731
53957	DEAGSEADHEGTHSTK	Fibrinogen alpha chain	0.55	709.99		0.82	528.6	1.34	0.6239371
60126	EEAPSLRPAPPPISGGGY	Fibrinogen beta chain	0.5	772.53		0.78	482.76	1.60	0.6108099
60628	LVDFEDNYQFAKYR	Ficolin-2	0.34	361		0.78	295.44	1.22	0.7151892
70456	YLWVGTGASEAEKTGAQEL	Gelsolin	0.16	498.15		0.47	654.13	0.76	0.6591199
32022	TYFPHFDLSHG	Hemoglobin subunit alpha	0.16	208.23		0.41	233.67	0.89	0.6230867
23423	VAHVDDMPNAL	Hemoglobin subunit alpha	0.08	194.2		0.31	98.15	1.98	0.6175595
62080	AVAHVDDMPNALSALSDL	Hemoglobin subunit alpha	0.14	1953.08		0.35	330.34	5.91	0.6080995
77236	SFPTTKTYFPHFDLSHGSA	Hemoglobin subunit alpha	0.36	282.02		0.19	106.8	2.64	0.6031037
41665	DGLAHLDNLKGTFA	Hemoglobin subunit beta	0.24	148.06		0.48	162.58	0.91	0.6134141
19046	PTSRYIHFP	Histone-lysine N-methyltransferase MLL4	0.31	231.33		0.18	277.13	0.83	0.5704719
29685	GSGSGWSSSRGPY	Hornerin	0.17	174.58		0.5	235.3	0.74	0.6759141
47285	IFPPSDEQLKSGTAS	Ig kappa chain C region	0.4	561.74		0.22	439.43	1.28	0.5973108
51865	FIFPPSDEQLKSGTA	Ig kappa chain C region	0.7	1293.45		0.75	1902.28	0.68	0.5999150
15216	TISRLEPED	Ig kappa chain V-III region NG9	0.49	1000.53		0.13	477.43	2.10	0.6974915
4845	GGSGAmGSmD	Immunoglobulin-like and fibronectin type III domain-containing protein 1	0.28	894.52		0.42	762.13	1.17	0.5813138
79918	LSDPEQGVEVTGQYEREKAG	Inter-alpha-trypsin inhibitor heavy chain H4	0.38	1497.08		0.17	1238.23	1.21	0.6107568
39607	DTDRFSSHVGGTLG	Inter-alpha-trypsin inhibitor heavy chain H4	0.57	751.39		0.71	730.22	1.03	0.5925808
44146	DDFDAHKALEDDE	Isoform 1 of Histone-lysine N-methyltransferase MLL2	0.16	301.07		0.47	429.11	0.70	0.6597577
54184	PGNPGPpGADGIAGAAGppG	Isoform 3 of Collagen alpha-1(XXII) chain	0.39	3263.92		0.24	3109.13	1.05	0.5836522
59773	LnEDAYmGVVDEATLQ	Izumo sperm-egg fusion protein 1	0.33	291.61		0.63	356.09	0.82	0.6704932

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
13746	ATKTVGSDTF	Kininogen-1	0.14	253.92		0.3	180.17	1.41	0.5742985
51838	GSqDGPVSNPSSSnSSQ	Liprin-alpha-1	0.1	226.47		0.35	427.2	0.53	0.6301020
93361	mASDASHALEAALEQMDGIIAGTK	Liprin-beta-2	0.21	151.65		0.39	183.1	0.83	0.5857249
49958	SGDSDDDEPPPLPRL	Membrane associated progesterone receptor component 1	0.34	578.89		0.85	739.65	0.78	0.7680697
44464	GDSDDDEPPPLPRL	Membrane associated progesterone receptor component 1	0.27	156.32		0.54	191.66	0.82	0.6420068
129131	GTSLSPPPESSGSPQQPGLSAPHSRQIPAPQGAV	Metastasis-suppressor KiSS-1	0.27	128.2		0.43	157.66	0.81	0.5900298
132057	GRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAPEV	Neurosecretory protein VGF	0.4	866.82		0.67	1219.88	0.71	0.6789966
140780	GRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAPEVRGA	Neurosecretory protein VGF	0.59	1264.38		0.67	1945.24	0.65	0.5944940
33938	NRDGPRQDTQAP	Nuclear pore complex protein Nup205	0.68	690.47		0.56	373.67	1.85	0.6341412
63517	EKETVIIPNEKSLQLQ	Osteoglycin	0.35	812.49		0.2	194.64	4.17	0.5848214
111426	IPVKQADSGSSEEKQLYNKYPDAVAT	Osteopontin	0.55	4883.89		0.25	3574.86	1.37	0.6565689
20700	YNKYPDAVAT	Osteopontin	0.22	147.49		0.46	213.25	0.69	0.6280825
47855	YKRKANDESNEHS	Osteopontin	0.43	527.24		0.66	750.62	0.70	0.6377551
30524	IQNWPHYRSP	Peptidoglycan recognition protein 1	0.34	657.07		0.19	250.05	2.63	0.5838648
73015	ELTETGVEAAAASAISVARTL	Plasma protease C1 inhibitor	0.51	433.53		0.23	90.09	4.81	0.6792092
60816	FAEEKAVADTRDQADGS	Polymeric immunoglobulin receptor	0.4	418.99		0.66	335.75	1.25	0.6109162
33812	DSGSSEEQGGSSRA	Polymeric-immunoglobulin receptor	0.23	217.57		0.63	234.65	0.93	0.7113095
136697	FAEEKAVADTRDQADGSRASVDSGSSEEQGGSSRA	Polymeric-immunoglobulin receptor	0.54	822.31		0.75	1181.43	0.70	0.6492347
55917	DHDVGSELPPEGVLGAL	ProSAAS	0.23	298.07		0.51	743.94	0.40	0.6503508
62323	YSQGSKGPGEDFRMATL	Prostaglandin-H2 D-isomerase	0.1	487.41		0.34	1767.57	0.28	0.6230867
63098	YSQGSKGPGEDFRmATL	Prostaglandin-H2 D-isomerase	0.19	568.26		0.43	959.79	0.59	0.6283482
58880	KmHEGDEGPGHHHKPG	Protein S100-A9	0.23	354.57		0.54	558.35	0.64	0.6673044
17830	VIEHIMEDL	Protein S100-A9	0.39	352.81		0.17	185.34	1.90	0.6222364
20204	DTNADKQLSF	Protein S100-A9	0.11	434.52		0.3	150.29	2.89	0.5950787

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
3608	KLGHPDTL	Protein S100-A9	0.23	135.29		0.36	148.8	0.91	0.5796662
44679	AHDYFKDTGGDGQD	Rab GTPase-activating protein 1	0.58	696.74		0.9	822.72	0.85	0.6905825
98720	REQGHQKERNQEmEEGGEEEH	Retinitis pigmentosa GTPase regulator	0.44	424.63		0.34	166.37	2.55	0.5856186
60751	SVDETGQmSATAKGRVR	Retinol-binding protein 4	0.86	2286.7		0.97	3288.38	0.70	0.6967474
38790	LQKGNDDHWIVD	Retinol-binding protein 4	0.45	474.69		0.33	257.3	1.84	0.5864158
123750	EGGVNHENGmNRDGGmIPEGGGGNQEPRQQ	Rhox homeobox family member 1	0.81	867.05		0.67	551.81	1.57	0.6302083
125103	SSQGGSLPSEEKGHPQEESEESNVSMASLGE	Secretogranin-1	0.16	159.05		0.44	208.66	0.76	0.6462585
74187	DAHKSEVAHRFKDLGEEN	Serum albumin	0.42	809.32		0.71	1202.1	0.67	0.6792092
17968	DGGGSPKGDVDP	Sodium/potassium-transporting ATPase subunit gamma	0.62	310.36		0.91	888.01	0.35	0.8322173
42404	GLSMDGGGSPKGDVDP	Sodium/potassium-transporting ATPase subunit gamma	0.38	336.54		0.75	655.59	0.51	0.7386267
49713	TGLSmDGGGSPKGDVDP	Sodium/potassium-transporting ATPase subunit gamma	0.11	310.87		0.36	186.14	1.67	0.6212266
48580	TGLSMDGGGSPKGDVDP	Sodium/potassium-transporting ATPase subunit gamma	0.57	657.3		0.79	972.89	0.68	0.6522109
43226	GLSmDGGGSPKGDVDP	Sodium/potassium-transporting ATPase subunit gamma	0.11	90.04		0.31	207.6	0.43	0.6078869
24660	YLGGSPKGDVDP	Sodium/potassium-transporting ATPase subunit gamma isoform 2	0.13	77.91		0.41	159.05	0.49	0.6491815
56099	REQGVEEHETLLLR	TLN1 Talin-1	0.23	404.84		0.45	221.12	1.83	0.5980548
25363	DAQSGSGQRSQP	Ubiquitin-associated protein 2	0.82	1060.15		0.77	1895.59	0.56	0.6034226
8503	SGSVIDQSR	Uromodulin	0.19	140.61		0.48	327.52	0.43	0.6712372
43605	SVIDQSRVLNLGPI	Uromodulin	0.5	7057.59		0.2	6131.35	1.15	0.6506696
14763	SGSVIDQSRV	Uromodulin	0.13	1498.96		0.34	336.22	4.46	0.6056016
58355	SGSVIDQSRVLNLGPIT	Uromodulin	0.76	6326.81		0.88	8174.64	0.77	0.6360544
11413	VLNLGPITR	Uromodulin	0.49	401.63		0.85	1006.41	0.40	0.7746599

ID	Sequence of Polypeptide	Protein Name	Cases			Controls		R	AUC
			%	MA		%	MA		
65035	SVIDQSRVLNLGPITRK	Uromodulin	0.44	916.62		0.21	565.49	1.62	0.6232993
44633	VIDQSRVLNLGPIT	Uromodulin	0.36	1404.38		0.63	2092.26	0.67	0.6359481
50056	SVIDQSRVLNLGPIT	Uromodulin	0.58	2617.31		0.4	2499.12	1.05	0.6105442
54438	VIDQSRVLNLGPITR	Uromodulin	0.83	13229.37		0.92	22414.37	0.59	0.6008716
59368	FGASAGTGDLSDNHDIIS	Vesicular integral-membrane protein VIP36	0.44	745.55		0.26	711.64	1.05	0.5986395
77684	FGASAGTGDLSDNHDIISMKL	Vesicular integral-membrane protein VIP36	0.35	1384.49		0.21	392.59	3.53	0.5846088
72033	FGASAGTGDLSDNHDIISMK	Vesicular integral-membrane protein VIP36	0.35	885.28		0.23	286.88	3.09	0.5825893
61984	DQDKHDDSTDDSDTDK	WW domain-binding protein 11	0.43	884.19		0.85	1510	0.59	0.7767857
50212	VGGGEQPPPAPAPRRE	Xylosyltransferase 1	0.57	383.1		0.79	315.83	1.21	0.6010842
99691	PEAEAEAEAGAGGEAAAEEGAAGRKARG	Zinc finger protein 653	0.47	288.62		0.35	155.64	1.85	0.5874787

ID, polypeptide identifier (SQL number); %, percentage of samples, in which the polypeptide could be detected; MA, mean signal amplitude of the polypeptides; AUC, area under the curve.
R was calculated as Σ (ln signal amplitude x frequency/number of participants) in controls divided by Σ (ln signal amplitude x frequency/number of participants) in cases. The polypeptides were ordered by ascending R. Polypeptides highlighted in red are collagen fragments.

Table S5. Amplitude of 20 shared polypeptides included in CKD273, HF1 and HF2 classifiers

Polypeptide	CKD273		HF1		HF2	
ID	Case	Control	Case	Control	Case	Control
1577	167.0	237.3	1.7	1.9	16.1	102.8
23697	630.2	930.8	2.8	2.9	241.5	786.9
26670	2430.6	4375.1	3.0	3.3	424.8	1614.6
28561	5641.3	8205.4	3.4	3.8	1399.0	6008.8
28747	12225.7	5492.4	3.4	3.3	9847.5	5184.5
35339	2970.2	4081.1	3.4	3.5	2120.7	3398.0
50840	6834.4	6183.1	4.2	3.9	8845.8	5676.2
57537	4911.8	5657.1	4.0	3.8	5458.5	5920.2
58050	682.2	576.0	2.6	2.8	184.5	373.8
60149	2047.2	2090.7	3.7	3.5	2229.7	2125.1
72533	2073.7	2003.5	3.5	3.2	2968.1	1625.5
79136	4523.0	5039.3	3.7	3.5	5153.1	4211.9
81196	5000.9	5005.7	3.7	3.6	6242.9	5197.3
82708	729.3	1169.3	2.6	2.7	198.5	593.5
90344	1897.5	2434.3	3.1	3.5	938.5	2364.7
99475	443.7	279.0	2.8	2.4	601.4	299.1
101157	235.8	162.1	2.0	2.0	10.8	38.1
104786	2625.4	2540.8	3.6	3.3	3500.1	2056.3
107460	1642.3	2042.2	2.9	3.1	791.1	1342.5
143947	428.9	769.6	2.3	2.2	86.7	210.4

Table S6. Host and lifestyle determinants of renal function in stepwise regression models in 797 participants

Explanatory variables	Serum creatinine	eGFR (MDRD)	eGFR (CKD-EPI)
	Estimate (95%CI)	Estimate (95%CI)	Estimate (95%CI)
Women (0,1)	–15.9 (–18.2, –13.6)§	…	…
Age (+15.7 years)	1.92 (0.79, 3.05)§	…	…
Smoker (0,1)	–2.80 (–5.07, –0.53)*	2.69 (–0.01, 5.38)	2.55 (–0.15, 5.26)
Waist-to-hip ratio (+0.08)	–1.33 (–2.62, –0.05)*	…	…
Mean arterial pressure (+10.7 mm Hg)	1.05 (0.03, 2.07)*	–3.17 (–4.34, –2.00)§	–3.98 (–5.15, –2.80)§
Blood glucose (+0.78 mmol/L)	…	…	–1.20 (–2.35, –0.05)*
Log γ-glutamyltransferase (doubling)	…	1.38 (0.06, 2.72)*	1.33 (–0.01, 2.68)
Total-to-HDL cholesterol ratio (+1.03)	1.91 (0.88, 2.93)‡	–1.46 (–2.62, –0.31)*	–1.70 (–2.87, –0.54)†
Log 24-h albuminuria (doubling)	1.87 (0.98, 2.77)§	–1.99 (–3.03, –0.95)‡	–2.45 (–3.51, –1.39)§
RAAS inhibitor (0,1)	…	–4.12 (–7.13, –1.10)†	–5.68 (–8.73, –2.64)‡
Vasodilator (0,1)	–5.30 (–9.52, –1.09)*	…	…
Diuretics (0,1)	8.27 (5.14, 11.4)§	–8.44 (–12.4, –4.50)§	–9.68 (–13.6, –5.73)§

Covariables considered for entry into the multiple regression models were sex, age and body mass index (only for serum creatinine) and for all renal function indices mean arterial pressure, waist-to-hip ratio, smoking, γ-glutamyltransferase (index of alcohol intake), total-to-HDL cholesterol ratio, blood glucose, 24–h albuminuria, and use of diuretics, vasodilators (calcium channel blockers and α-blockers), and inhibitors of the renin-angiotensin system (β-blockers, angiotensin-converting-enzyme inhibitors, and angiotensin receptor blockers). For continuous variables, effect sizes are expressed for a 1–SD increase or a doubling for logarithmically transformed variables. The percentage of variance explained by the whole model was 34.7%, 14.6%, and 22.4% for serum creatinine, eGFR (MDRD), and eGFR (CKD-EPI), respectively.
Significance: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$; and § $P \leq 0.0001$.

Table S7. Change in eGFR classification during follow-up in 621 participants

		Baseline				
		Stage	**1**	**2**	**3**	**4**
MDRD	**Follow-up**	**1**	34	13	0	0
		2	88	394	11	0
		3	1	48	29	0
		4	0	1	1	1
CKD-EPI	**Follow-up**	**1**	82	17	0	0
		2	110	317	6	0
		3	0	53	31	0
		4	0	1	3	1

Cross-classification of CKD stages according to the eGFR at baseline and follow-up as computed by the MDRD and CKD-EPI formulas in 621 participants.

Table S8. Multivariable-adjusted hazard ratios relating endpoints to the urinary proteomic biomarkers in 797 participants

Endpoint (number of events)	Model	Hazard ratios (95% Confidence interval)			
		CKD273	HF1	HF2	SF
Cardiovascular events (*n* = 47)	1	1.15 (0.87, 1.52)	1.29 (0.98, 1.69)*	1.41 (1.07, 1.86)†	1.33 (1.01, 1.74)†
	2	1.15 (0.87, 1.52)	1.29 (0.98, 1.69)*	1.41 (1.07, 1.86)†	1.33 (1.01, 1.75)†
	3	1.14 (0.85, 1.52)	1.28 (0.98, 1.69)*	1.40 (1.06, 1.86)†	1.32 (1.01, 1.74)†
	4	1.14 (0.85, 1.52)	1.29 (0.98, 1.69)*	1.40 (1.06, 1.86)†	1.32 (1.00, 1.74)†
Cardiac events (*n* = 29)	1	1.22 (0.86, 1.73)	1.41 (1.00, 1.99)†	1.32 (0.92, 1.89)	1.37 (0.97, 1.92)
	2	1.21 (0.85, 1.72)	1.40 (0.99, 1.97)*	1.31 (0.91, 1.89)	1.35 (0.96, 1.90)
	3	1.24 (0.86, 1.79)	1.41 (1.00, 1.99)†	1.32 (0.91, 1.90)	1.37 (0.97, 1.94)
	4	1.23 (0.85, 1.78)	1.40 (0.99, 1.97)*	1.32 (0.92, 1.91)	1.36 (0.97, 1.93)

Hazard ratios, given with 95% confidence interval, express the increase in risk associated with a 1–SD increase in the explanatory variables derived from the urinary proteome. SDs were 0.39 for CKD273; 0.92 for HF1; 0.62 for HF2; and 1.0 for SF. The covariables accounted for in model 1 were sex, age, mean arterial pressure, body mass index, waist-to-hip ratio, smoking, log γ-glutamyltransferase (index of alcohol intake), total-to-HDL cholesterol ratio, and blood glucose. Models 2, 3, and 4 were additionally adjusted for baseline eGFR according to the MDRD formula, baseline 24–h albuminuria, or both.
Significance of the hazard ratios: * $0.05 \le P \le 0.07$; † $P < 0.05$.

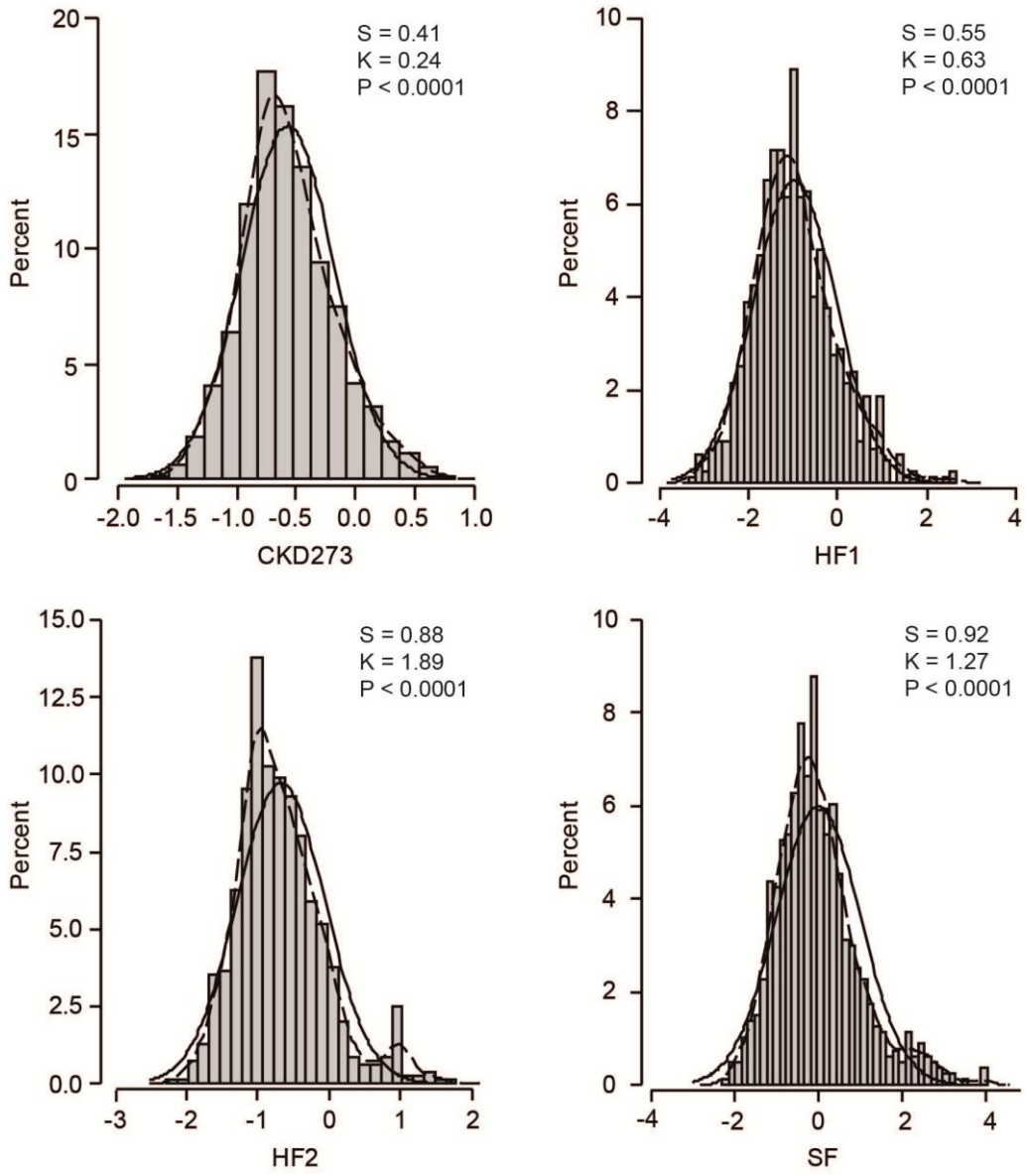

FIGURE S1. Frequency distributions of CKD273, HF1, HF2 and SF at baseline in 797 participants. S and K are the coefficients of skewness and kurtosis. The P value is for departure of the actually observed distribution (kernel distribution; dotted line) from normality (full line).